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The American Heart Journal

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Original Communications

DYNAMIC DILATATION OF THE THORACIC AORTA*

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DYNAMIC dilatation of the aorta may be defined as an increase in the size of the lumen for a variable distance along its course, without structural disease of the aortic wall. The systolic excursion of the aorta is usually increased. The enlargement is ordinarily maintained throughout diastole, and is thought to be the mechanical result of cardiovascular factors. It must be understood that disease at the site of dilatation does not exist to an influential degree or the condition at once becomes confused with aneurysm, aortitis or arteriosclerosis.

Osler[1] stated that dynamic dilatation of the aorta was first observed in the time of Morgagni, and describes its occurrence in three conditions: aortic insufficiency, neurotic states, and anemia.

In 1886 Hare[2] reported a most instructive case as aneurysm of the thoracic aorta. A white girl, aged eighteen years, came under his observation complaining of pain in the left chest and arm. She had suffered from attacks of acute articular rheumatism every winter for six or seven years. "Inspection of the chest showed an egg-shaped protrusion in the suprasternal notch, very expansile and bulging at each systole of the heart. Dilatation extended well up the innominate artery for over one inch from its point of origin. . . . Over the protrusion was a thrill and bruit." There was a double aortic murmur and a water-hammer pulse. Osler, who saw the patient during life, stated that at autopsy a few months later, he was not surprised at finding the lumen of the aorta too small to admit the index finger.

Sheldon[3] observed the condition in a boy, ten and one-half years old, who suffered from chronic nephritis with hypertension and secondary anemia. The blood Wassermann test was negative on two occasions. The systolic blood pressure was 210 mm. Hg; the diastolic, 155 mm. Hg.

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An aortic diastolic murmur developed while the patient was under observation. Roentgen-ray studies demonstrated pronounced enlargement of the aortic arch. The child died of uremia a month later. Autopsy showed an aortic arch of normal size. Sheldon cites a similar case described by Evans;[4] this patient, a child, died of cerebral hemorrhage. These three cases are unquestionable examples of dynamic dilatation of the thoracic aorta. Navarrow[5] in 1917 reported a probable case. The patient was a child with rheumatic aortic insufficiency. Syphilis was excluded. Under observation the aortic arch dilated from a position 1 cm. to a position 3 cm. above the suprasternal notch. Navarrow suggested that rheumatic disease may affect the aorta as does syphilis.

Compare with this group the cases of permanent enlargement of the cavity of the aorta, due to syphilis and arteriosclerosis reported by McCrae,[6] Brown,[7] and Lankford.[8] This condition most commonly involves the ascending aorta. It was described by Hodgson in 1815 and is referred to as the Maladie de Hodgson by the French. Unlike dynamic dilatation it is due to disease of the aortic wall, either arteriosclerosis or syphilis, or both. The disease process frequently involves the aortic valve. Until the advent of the x-ray this type of aortic enlargement was almost always an unsuspected finding in the dead house. With modern x-ray methods its detection is common. As might be suspected the patients are almost without exception over thirty-five years of age. Two of McCrae's cases were under thirty years of age, and, therefore, may not have belonged to this group. The enlargement is of fusiform character and involves the arch of the aorta and is always in evidence at autopsy with accompanying disease of the vessel wall.

CASE REPORTS

The three following cases were studied on the wards of the University of Michigan Hospital. All were seen within a period of two months.

CASE 1.—A housewife, white, aged thirty years, was admitted to the medical ward Jan. 8, 1932, complaining chiefly of pain in the precordium and in the right side. These pains were not associated, the latter being felt in the right costovertebral angle. She was known to have had a "leaking heart" at the age of twelve years. At fifteen years she had a typical attack of rheumatic fever. She thought that this aggravated the heart condition, as at that time she experienced shortness of breath on exertion. The precordial pain, although present for the past eight years, had become more severe during the past year. It was most intense at the apex of the heart. Its onset was sudden and was accompanied by numbness of the left arm, tachycardia and flushing of the face and neck. She had noticed edema only during pregnancies. She was the mother of four children and had had considerable domestic difficulty.

Physical Examination.—The patient was asthenic and did not appear acutely ill. There was no orthopnea or dyspnea at rest. The pupils were round, regular, equal, and reacted to light and in accommodation. The apex impulse was seen and felt in the fifth intercostal space, 7.5 cm. from the midsternal line. It was well localized and not abnormally forceful. There was visible systolic pulsation

in the right second intercostal space just lateral to the sternal border, more pronounced during full expiration and after exertion. It was not palpable and there was no thrill. At this level the supracardiac dullness extended 4 cm. to the right of the midsternal line. The left border of cardiac dullness extended 8 cm. to the left of the midsternal line in the fifth intercostal space. A soft systolic murmur was heard at the apex. In the aortic area was a high-pitched diastolic murmur of medium intensity which replaced the second sound. The pulmonic second sound was not accentuated. The systolic blood pressure was 138 mm. Hg; the diastolic, 72 mm. There was no Corrigan pulse, nor were there other vascular signs of aortic insufficiency. The lungs were clear. There was tenderness in the right costovertebral angle. The right kidney was palpable and movable.

Laboratory Tests.—The routine Kahn test for syphilis was negative on two occasions. The routine urine, blood, and stool examinations showed nothing abnormal. The electrocardiogram showed marked left ventricular preponderance. The x-ray studies, including fluoroscopic examination, showed a gross increase in

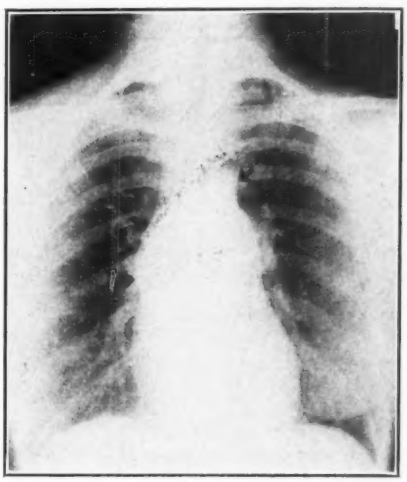

Fig. 1.—Case 1. Pronounced increase in the supracardiac shadow, due to dynamic dilatation of the aorta in a case of aortic insufficiency (probably rheumatic in origin). Boundary of aortic shadow marked by arrows.

the anteroposterior diameter, as well as in the transverse diameter (Fig. 1) of the ascending aorta without cardiac enlargement. The transverse and descending portions of the aorta were thought not to be dilated. The patient had no attacks of chest pain during the four weeks that she remained on the medical ward, although she was up and about during the last half of this period. She returned three months later for a check-up. No drugs had been taken in the interim. Further x-ray studies at this time showed no change in the size of the heart or aorta.

Discussion.—Syphilis with aortitis and aneurysm and rheumatic heart disease were the cardiovascular diagnoses considered. It was apparent clinically that a large part of the precordial pain was psychogenic. The patient apparently desired hospitalization to escape domestic routine. The only "heart attack" occurred in the convalescent hospital pending discharge from the surgical service where the diagnosis of nephroptosis

had been made. The pain of syphilitic aortitis is usually substernal rather than apical and is not as a rule accompanied by rapid heart action. Under the fluoroscope the lively pulsations of the first part of the aorta were striking. The enlargement apparently involved the entire circumference of the vessel. When the pulsation of an aneurysm is visible, it is usually palpable as well. Since the patient was known to have a valve lesion at twelve years of age, it is improbable that syphilis could have been the causative factor. The definite history of rheumatic fever strongly suggests that this condition was alone responsible for the lesion. Rheumatic aneurysm is relatively rare, and it is of the mycotic type which is quite incompatible with the picture presented. In view of the observations described later, it seems probable that the dilatation of the aorta was of the dynamic variety, and one would not expect to find the vessel enlarged post mortem.

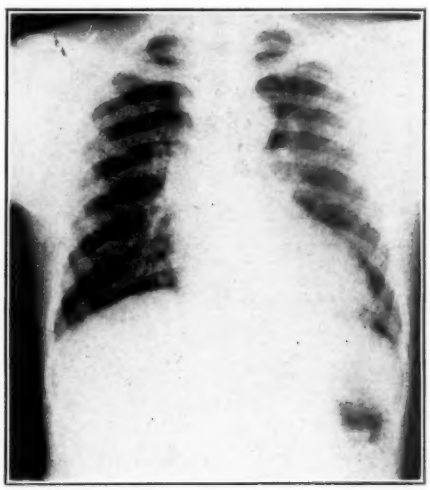

Fig. 2.—Case 2. Dynamic dilatation of the aorta and pronounced enlargement of the heart, involving the left ventricle particularly. Limits of aortic shadow marked by arrows; the point indicated pulsated violently on fluoroscopic examination, and aneurysm was suspected.

Case 2.—A boy, aged fourteen years, was admitted to the medical ward on Feb. 8, 1932, complaining chiefly of a head cold. Head colds and sore throat had occurred frequently for several years. At the age of eight he was told he had heart disease. His activities had been restricted since. The present respiratory infection had troubled him for four weeks and was accompanied by sore throat and fever. There was no history of rheumatic fever or chorea.

Physical Examination.—The patient was delicately built, well nourished, and not acutely ill. The pupils were equal and reacted to light and in accommodation. There was slight pulsation of the retinal arteries. There was considerable carotid pulsation at the angles of the jaw. The neck veins were not distended. Systolic pulsation was seen in the suprasternal notch and in the right second intercostal space close to the sternum. The apex impulse was in the anterior axillary line at the level of the fifth intercostal space. The left border of cardiac dullness was 13 cm. and the right border 3.5 cm., from the midsternal line. The

supracardiac dullness measured 7 cm. in width. There was a thrill at the apex and base. A double aortic murmur was present. At the apex there was a loud harsh systolic murmur and an early diastolic rumble. The pulmonic second sound and the mitral first sound were accentuated. The rhythm was regular. The heart rate was 104 per minute. The systolic blood pressure was 130 mm. Hg; the diastolic 40 mm. Hg. There was a suggestive Corrigan pulse, and a pistol-shot sound was audible over the femoral vessels. The lungs were clear. The abdomen and extremities were negative. The reflexes were active.

Laboratory Tests.—The routine Kahn test was negative. The blood, stool, and urine studies showed nothing abnormal. The electrocardiogram showed extremely tall QRS deflections. The T-waves were diphasic in Lead II and inverted in Lead III, as is frequently the case in aortic insufficiency with great cardiac enlargement. The orthodiagram showed a variation of plus 30 per cent in the frontal plane area (as compared with the normal for individuals of similar height and weight), and plus 39 per cent in the transverse diameter of the cardiac silhouette. X-ray studies (Fig. 2) showed gross prominence of the aortic knob and widening of the ascending aorta; cardiac enlargement, chiefly left sided; and thickening of the apical pleura on the right side. Lateral plates confirmed the diagnosis of aortic dilatation.

Clinical Course.—The patient remained in the hospital four weeks on bed rest. There was slight fever and leucocytosis, possibly due to active endocarditis. Prolonged rest was advised on discharge.

Discussion.—The aortic dilatation in this case was more diffuse than that in Case 1 and involved the entire aortic arch. On fluoroscopic examination the size and pulsations of the aorta were striking. The examiner's first remark was "aneurysm." The marked enlargement of the left ventricle is apparent in the x-ray plate (Fig. 2).

CASE 3.—A white boy, aged seventeen years, was admitted to the medical service on Feb. 11, 1932, complaining chiefly of shortness of breath and pounding of the heart. There was a history of rheumatic fever six years before. No history of congestive cardiac failure.

Physical Examination.—The boy was fairly well developed, but his nutrition was poor. The cheeks presented a malar flush and the lips a reddish cyanosis. The left pupil was slightly larger than the right. There was moderate overdistention of the veins of the neck and vigorous throbbing of the carotid arteries. The precordium was prominent and the cardiac apex pounded forcibly in the midaxillary line. All the classical signs of mitral stenosis and aortic insufficiency were present. The supracardiac dullness extended 7.5 cm. to the right of the midsternal line at the level of the second intercostal space. In this space there was a visible systolic pulsation followed by a diastolic thrill. The rhythm was regular; the heart rate 100 per minute. The systolic blood pressure was 120 mm. Hg, the diastolic 40 mm. The lung fields were clear. The liver border reached two finger breadths below the right costal margin. The remainder of the examination contributed nothing of importance.

Laboratory Tests.—The routine blood Kahn test was negative. The blood, stool, and urine findings were not abnormal. The electrocardiogram showed marked inversion of the T-waves in Leads I, II, and III, suggesting myocardial changes. X-ray studies (Figs. 3 and 4) showed widening of the thoracic aorta and prominence of the soft tissues of the neck, suggesting involvement of the innominate, common carotid and subclavian arteries as well. The orthodiagram showed a plus 48 per cent variation in the frontal plane area (in comparison with normal stand-

ards for individuals of like height and weight) and a plus 47 per cent variation in the transverse diameter of the cardiac silhouette.

Clinical Course.—The patient remained in the hospital four weeks. The systolic blood pressure varied from 100 to 120 mm. Hg, the diastolic rose steadily from 40 mm. Hg on admission to 80 mm. at the time of discharge.

Discussion.—The general picture resembled that seen in Case 2 in many respects. One might even have mistaken it for a more advanced stage of the underlying process in the same individual. The dilatation of the aortic arch was extreme. The right border of the ascending aorta lay just inside the right midclavicular line. There were no symptoms of superior mediastinal compression. It is interesting to speculate on the possibility that the left pupillary enlargement resulted from stimulation of the left thoracic sympathetic nerve trunk by the large vigorously pounding thoracic aorta. More interesting still was the

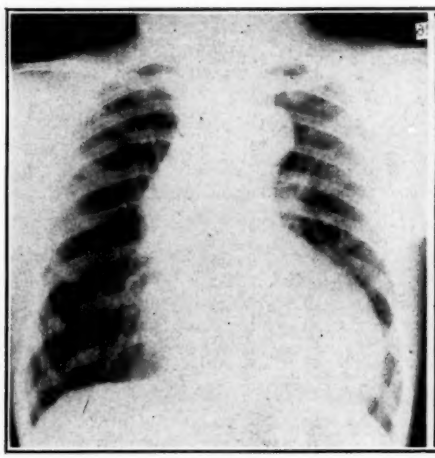

Fig. 3.

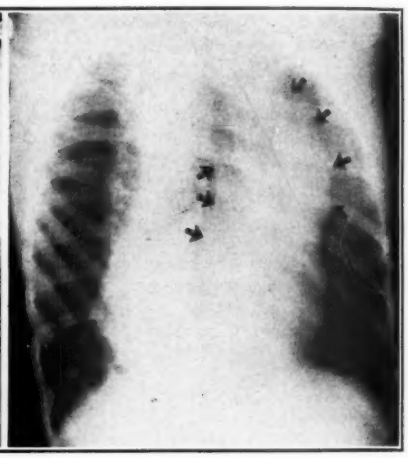

Fig. 4.

Fig. 3.—Case 3. Dynamic dilatation of aorta and its main branches. Great enlargement of heart.

Fig. 4.—Case 3. Cardiac silhouette, right anterior oblique view. Outline of enlarged ascending aorta indicated by arrows.

steady rise of the diastolic blood pressure during hospitalization. Surely such mechanical improvement could not have been due to actual healing of the pathological changes in the aortic valve, for such healing ordinarily results in greater insufficiency or stenosis. It seems probable that the steady rise of 40 mm. Hg in the diastolic pressure was due to improvement of a superimposed relative insufficiency of the aortic valve, associated with the extreme aortic dilatation.

OTHER CASES OF RHEUMATIC AORTIC INSUFFICIENCY

Eighty cases of rheumatic aortic insufficiency were selected from the hospital records for study. In order to avoid including examples of luetic or arteriosclerotic aortic insufficiency unwittingly, all cases in

which the patient was more than thirty-one years of age were excluded.

Syphilitic aortic disease is rare in the age interval with which we are concerned. In the past seven years no cases of syphilitic aneurysm have been observed in this hospital in which the patient's age was less than thirty-one years. This condition has been observed in patients less than thirty-five years of age only six times during the same period. In all of these patients serological tests for syphilis were positive, and there was a history of syphilitic infection or of symptoms suggesting it. In all instances precordial pain was the chief complaint.

In 98.8 per cent of the eighty cases of rheumatic aortic insufficiency studied, the additional clinical diagnosis of mitral stenosis had been made. All of the patients had x-ray studies, and all gave negative serological tests for syphilis. Eight and four-tenths per cent were found to have definite enlargement of the aortic arch. Twenty com-

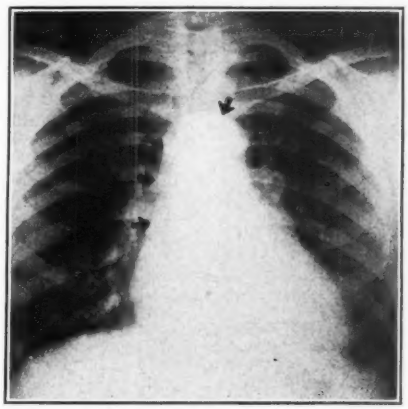

Fig. 5.—Cardiac silhouette in a case of rheumatic aortic insufficiency in which a hypoplastic aorta was found post mortem. The borders of the aortic shadow are indicated by arrows.

plained of pain that could be ascribed to cardiovascular disease. The pain seemed to be dependent upon the grade of heart failure. No patients complained of severe, unbearable pain who were not on the verge of advanced congestive heart failure. Pathological studies in cases in which death occurred during an acute attack of rheumatic fever have shown that acute rheumatic aortitis is present in the majority.[10] Precordial pain is not a usual complaint of patients weathering an acute rheumatic attack unless pericarditis or pleuritis develops. It would seem that acute rheumatic aortitis does not commonly produce pain. It is fairly well established that rheumatic disease of the aorta is confined chiefly to the adventitia with minute intimal changes.[11] The media, though affected during the acute stage, undergoes no changes even remotely resembling those of syphilis. It is for this reason that rheumatic aneurysm is invariably of the mycotic type.

In this group of eighty patients the average systolic blood pressure was found to be 129 mm. Hg; the average diastolic was 71 mm. The heart rate was so variable that an average would mean little or nothing. Only 64 per cent of the patients with an enlarged aorta had a pulse pressure greater than the average. In this series of cases of rheumatic aortic insufficiency there was one with clinical enlargement of the aorta (Fig. 5) that came to autopsy. The aorta was found to be hypoplastic post mortem.

The healing of the acute aortitis that must accompany most of the severe cases of rheumatic fever is apparently complete in the vast majority. This is shown by a study of 64 autopsied cases of rheumatic heart disease, only one of which showed microscopic evidence suggesting rheumatic aortitis. This series of autopsied cases, included cases with either aortic or mitral lesions or with both. In no instance was the aorta enlarged. Nineteen per cent of the patients with aortic insuf-

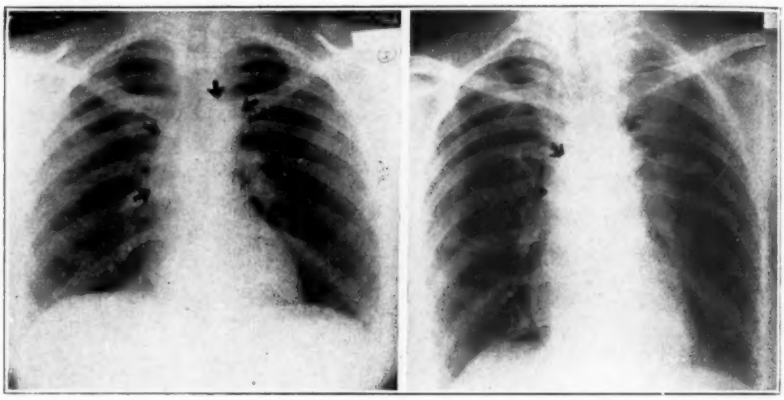

Fig. 6. Fig. 7.

Fig. 6.—Dynamic dilatation of the aorta in a patient with cardiac symptoms attributed to a psychoneurosis.

Fig. 7.—Dynamic dilatation of the aorta in a young psychoneurotic patient. Outline of aorta indicated by arrows.

ficiency with or without mitral stenosis had hypoplasia of the aorta. A clinical diagnosis of aneurysm was made in 3 per cent of the cases, and in each instance aortic insufficiency was present. In no case was an aneurysm found post mortem. It was rather interesting to note that 16 per cent of the cases diagnosed clinically as having aortic insufficiency and mitral stenosis were shown after death to have aortic insufficiency without organic mitral stenosis.

EXOPHTHALMIC GOITER

Two hundred and sixty-three cases of exophthalmic goiter were selected. There was no evidence that any of the patients had syphilis. All were between fourteen and thirty-one years of age. All had had x-ray studies. It was found that 12 per cent had enlargement of the

aortic arch. Of this number only one complained of pain that could be attributed to heart disease.

The aortic enlargement in this group was not as striking as in the rheumatic group. Prominence of the aortic knob was the common finding, although widening of the base of the aorta and violent pulsations were observed on a few occasions. The average pulse pressure was 72 mm. Hg. One of the patients with clinical enlargement of the aorta died of pneumonia, and the aorta was hypoplastic at autopsy.

CARDIAC NEUROSIS

The case records of thirty-one patients between fourteen and thirty-one years of age with cardiac complaints that were attributed to a psychoneurosis were examined. In none of these cases was there any evidence of syphilitic infection. Roentgen-ray examinations had been made in all. In three, or 9 per cent, there was definite enlargement of the aortic arch as determined by x-ray and fluoroscopic examination. (Figs. 6 and 7.) Two-thirds of the total number of patients complained of precordial pain. Aside from pain, sinus tachycardia was the only cardiovascular symptom. The electrocardiogram showed nothing abnormal except rapid heart action. The basal metabolic rates were all within the average normal limits. Foci of infection were not in evidence.

DISCUSSION

The literature on the subject of dynamic dilatation of the aorta was found to be surprisingly scanty; the condition is not well understood. It would seem that enlargement of the aortic arch is not uncommon in young persons affected with rheumatic aortic insufficiency, exophthalmic goiter, or a cardiac neurosis. That it also occurs in young persons with chronic nephritis and hypertension is shown by Sheldon's case already mentioned. On a few occasions I have observed striking enlargement of the aortic arch in a young person with pulmonary tuberculosis.

Dynamic dilatation of the aorta appears to depend upon various alterations in cardiovascular dynamics, but the exact manner in which it is brought about is not clearly understood. The age of the patient, sinus tachycardia, an increase in pulse pressure, an increase in the force and in the quantity of blood ejected by left ventricular systole and an increase in peripheral resistance are all thought to be important factors. Nutritional and toxic states may play a part in its development.

CONCLUSION

In young individuals an alteration in the normal cardiovascular dynamics may bring about an enlargement of the aortic arch. The enlargement may be pronounced and may induce a relative insufficiency of the aortic valve. In patients with a cardiac neurosis the dilated

aorta has been observed to return to normal size within a few weeks.[12] This so-called dynamic dilatation is manifest clinically, but not at autopsy. The condition is far more common than the literature would indicate, and is of great importance because of the frequency with which it is mistaken for aneurysm. Aortic enlargement of this type is commonly labeled aortitis, although no inflammation or organic disease of the vessel exists. The term aortitis so used is therefore misleading. In older people with aortic dilatation the diagnosis of aortitis is usually correct, for here autopsy reveals fusiform enlargement and degenerative changes. When syphilitic infection is known to have occurred and substernal pain, paroxysmal nocturnal dyspnea and a ringing aortic second sound are present, the diagnosis of aortitis may be justified even when x-ray examination is negative.

One should hesitate to make the diagnosis of aortitis or aneurysm in young individuals simply because the aorta is enlarged; the enlargement is likely to be of the dynamic sort.

Thanks are given to Dr. Frank N. Wilson for his invaluable assistance.

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A STUDY OF LEAD IV

Its Appearance Normally, in Myocardial Disease, and in Recent Coronary Occlusion*†

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WOLFERTH and Wood[1] recently described a fourth lead with which they found changes diagnostic of coronary occlusion that were absent in the three-lead electrocardiogram. This work shows that important electrocardiographic changes may be missed because they occur in the anteroposterior diameter, which the ordinary leads do not explore. In a second report, Wolferth and Wood[2] added three further cases of coronary occlusion in which the fourth lead was not essential for the diagnosis, and in one of which the fourth lead was not abnormal.

We decided to study this fourth lead further in order to define the normal configuration and the deviations from normal which might occur in a series of unselected consecutive cases. In this way we hoped to determine the value of using the fourth lead routinely.

Various tri-dimensional leads have been used experimentally (Cohn,[3] Wilson,[4] Zeisler and Katz[5]) but we decided to follow the Lead IV already studied by Wolferth and Wood.[1] Any other fourth lead which tapped the heart current in the anteroposterior plane would have served as well, but at this time it would be confusing to use another lead when a standard had been established. Indeed, in following their procedure we were tempted to reverse the connections of the electrodes because the normal configuration of Lead IV so taken, is like that of the other leads.

A series of 25 normals was obtained for control. Then, during June, 1932, this lead was used routinely on 86 patients with clinical evidence of heart disease, who were sent to the Heart Station for electrocardiograms. In addition, tracings of 11 patients with recent coronary occlusion were taken, in one of whom the diagnosis was confirmed by necropsy.

The series of tracings is too small to draw final conclusions on many points. We feel justified in presenting our tentative conclusions to serve as a basis for the normal and for deviations from normal. It will be seen, however, that the material is adequate to settle many points.

*Aided by a grant from the Herbert L. Celler Fellowship Foundation, New York, and by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

†From the Heart Station, Michael Reese Hospital, Chicago.

TECHNIC

The technic of Wolferth and Wood[1] was modified slightly. The patient lay on his left side. Pliable pure tin electrodes, 3 cm. by 8 cm., were employed. The site of the electrodes was shaved when necessary. The skin over the region was cleansed with alcohol. A warm paste of flour and salt was spread over the electrodes, which were then quickly applied to the chest. The anterior electrode was placed at the level of the fourth interspace just to the left of the sternum. The posterior electrode was placed on the back directly opposite the anterior electrode, viz., 180° from it, just medial to the right scapula. The anterior electrode was connected to the right arm terminal and the posterior electrode to the left arm terminal of the control box. The plates were kept close to the body, either with pillows or an elastic webbing.

The small size of the electrodes made it necessary to use precautions to keep the skin resistance low, by brightly polishing the electrodes, removing greasy material from the skin, increasing local circulation with warmth, making close contact with the skin and by using a concentrated salt-flour paste. Even with these precautions a few of our tracings showed overshooting. We discarded all tracings which showed, when standardized, an overshooting of more than 1.5 mm.

Our cases fell into three groups: (1) those showing no evidence of heart disease clinically or electrocardiographically (in the ordinary three leads); (2) those with clinical evidence of cardiac disease (a) with normal configuration in the standard three leads, (b) with abnormalities in these three leads indicating myocardial damage; and (3) cases of recent coronary occlusion. The appearance of Lead IV in each of these groups will be described in turn. The description is based on a detailed analysis of a large summary table of the measurements of all four leads in each case of the series.

NORMAL APPEARANCE OF LEAD IV

The Lead IV of the individuals who had no manifest cardiac pathological condition and whose three-lead electrocardiogram was normal, showed the following (Table I): (1) The P-wave was usually negative, often notched, and occasionally diphasic. (2) The P-R interval was generally shorter by 0.01 to 0.03 sec. than in Lead II (the usual lead in which the P-R is measured). (3) The QRS was diphasic, the first phase being negative, or if one prefers, a Q-wave in the sense of Pardee.[6] The QRS was high as a rule (average 20 mm.). The relative magnitude of the two phases of QRS varied considerably. In no instance was the QRS entirely negative or positive; as a rule the smaller phase was more than 15 per cent of the larger, and usually the two were of equal magnitude. In no instance was the first phase of the diphasic QRS positive. As a rule there was slight slurring of the downstroke of the Q-wave and of the positive wave. (4)

The S-T segment was usually isoelectric, but sometimes it was depressed as much as 2 mm. It was never elevated. Often the S-T interval could not be definitely distinguished, for the T-wave took off directly from the QRS. The S-T segment in many cases was curved. (5) The T-wave was inverted, as a rule, often peaked, with symmetrical sides

TABLE I

ANALYSIS OF LEAD IV IN 25 NORMAL CASES

	AVERAGE	LEAST	GREATEST
Height of P	−¾ mm.	+½ mm.	−1½ mm.
Duration of P	0.08 second	0.04 second	0.12 second
P-R interval	0.155 second	0.12 second	0.20 second
QRS duration	0.08 second	0.07 second	0.09 second
Amplitude QRS*	20 mm.	5 mm.	34 mm.
Height of Q	−8½ mm.	−1 mm.	−19 mm.
Height of positive portion of QRS	+12 mm.	+2 mm.	+33 mm.
Height of T	−3 mm.	+1 mm.	−8 mm.
Duration of T	0.18 second	0.07 second	0.25 second
S-T deviation	−1 mm.	0 mm.	−2 mm.

*Amplitude of QRS is the sum of the amplitudes of its two phases.

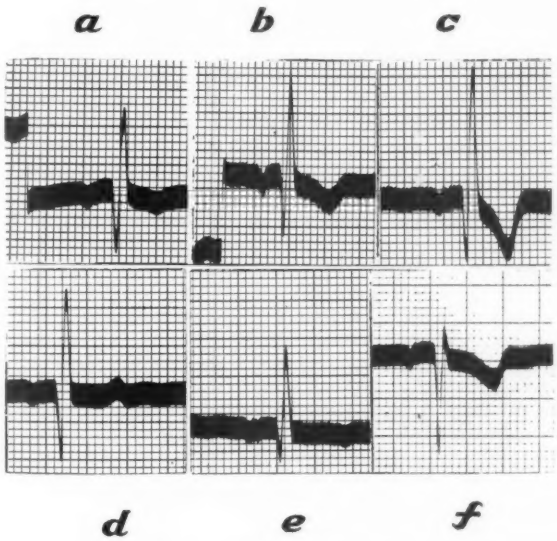

Fig. 1.—Six examples of normal Lead IV to show the range of variations in the QRS complex and in the T-wave.

and rounded shoulders, the convexities pointing upward and toward each other; an appearance which resembled the inverted coronary T-wave. In one case the T-wave was small and diphasic. (6) Occasionally an inverted U-wave was present. (7) The durations of P, QRS, and QRST in Lead IV were identical, within 0.02 to 0.03 of a second, with the meas-

urements in the other three leads (cf. Zeisler and Katz[5]). Segments of Lead IV in six normal cases are shown in Fig. 1.

LEAD IV IN PATIENTS WITH EVIDENCE OF CARDIAC DISEASE

The analysis is based on 86 tracings of all four leads in patients with evidence of heart disease other than recent coronary occlusion. Only 33 of these 86 records of Lead IV showed characteristics differing from the normal standards given above—the rest presented no deviation from normal. In general, our analysis showed that when the electrocardiogram of the three leads was within normal limits, it was also normal in Lead IV; when the curves of the standard three leads were abnormal, Lead IV was abnormal. A sufficient number of exceptions were present to warrant further analysis.

The time relationships are the same in Lead IV as in the other leads, viz., the duration of the P, the QRS, and the T in Lead IV, was found to be the same as in the other three leads. Two cases of bundle-branch block, for example, showed the identical widening of the QRS complex in all four leads. The P-R interval in first degree A-V block was also increased in Lead IV.

The arrhythmias, auricular fibrillation, A-V block, intraventricular block, sinus arrhythmia and shifting pacemaker, showed up as well in the fourth lead as in the conventional three. The "f" waves of auricular fibrillation were not always clearer in the chest lead than in the other leads (cf. Lewis[7]). In one instance Lead IV showed sino-auricular block when the others did not. It is likely that this phenomenon is due to the different position of the patient during the recording of Lead IV. The same explanation probably holds for those cases in which extrasystoles appeared in Lead IV but not in the other three leads.

Changes in QRS.—For this study the amplitude of the QRS complex was considered as the sum of the maximum deviation above and below the isoelectric line. The amplitude of the QRS complex so measured in Lead IV bore no definite relation to the amplitude in the other leads in this group of cases and in the normal series. Usually the amplitude in Lead IV was higher than in Leads I, II, III, but sometimes the reverse was true. "Low voltage" of the QRS in the conventional leads was not always accompanied by a "low voltage" in Lead IV as shown in Table II; the deflection often being normal, or even exceptionally high in this lead. Two tracings in our series showed a low deflection of QRS in Lead IV with deflections of normal amplitude in Leads I, II and III. These observations are summarized in Table II, in which QRS heights in Leads I, II and III of less than 10 mm. are compared with the QRS amplitude in Lead IV, and amplitudes of QRS of less than 10 mm. in Lead IV are compared with the amplitudes in the other leads. This lack of correlation is not difficult to understand. It has been pointed out (Katz[8]) that low amplitude in the standard three leads may be due to one of three causes: (a) intraventricular block, (b)

relative increase in the shunting of the heart's currents away from the electrodes, and (c) a change in the heart's position so that its long axis lies in a plane more nearly perpendicular to the plane of the leads. It is likely that the change in the position of the heart explains the lack of correspondence of the amplitude in Lead IV to that in the ordinary three leads. Lead IV may therefore be useful in separating cases of "low voltage" in the standard leads due to change in position, from those due to intraventricular block or increased body shunting.

TABLE II

CORRELATION OF AMPLITUDES* OF QRS IN THE FOUR LEADS

LEAD I	LEAD II	LEAD III	LEAD IV
11 mm.	7 mm.	8 mm.	3 mm.
16	6	12	4
11	8	4	9
4	5	5	8
5	5	2	8
5	4	2	6
6	5	3	9
4	8	7	6
7	7	2	10
3	7	5	10
4	4	2	15
1	5	3	11
4	2	3	15
4	3	5	14
6	7	4	19
4	6	2	13
5	5	6	14
3	9	5	16
7	8	2	19
8	8	4	16
3	9	6	16
6	4	3	17
7	7	8	16
6	5	7	18
6	3	7	15
6	3	8	18
5	9	4	14
5	4	5	20
6	3	5	21
4	8	6	43
8	5	6	22
7	9	3	36
7	5	6	24
9	5	4	41
8	9	7	27
8	7	5	20
8	3	6	21
3	8	6	22
8	8	3	21
4	3	9	21

*Amplitude of QRS is the sum of the amplitudes of its two phases.

Some slight slurring was present almost regularly in the routine Lead IV. The downstroke of the initial negative deflection and the downstroke of the terminal positive deflection were of less steep gradient and thicker than the upstroke. Occasionally an abnormal degree of slurring, or even notching, appeared in Lead IV without a similar change in the ordinary leads. More often, however, slurring or notching appeared in either Lead I or II but not in Lead IV. In a few instances we found excessive slurring and notching in all leads. In other words, excessive slurring might appear in Lead IV when not present in the other leads, and it might be absent in Lead IV when present in the other leads. Notching and slurring in Lead IV, but not in Leads I or II, occurred six times. In all of these there were clinical evidences of myocardial disease. Slurring or notching of Lead IV as an isolated finding therefore suggests cardiac disease; but no more significance can be attached to it than to isolated slurring or notching of QRS in either Leads I or II.

In no instance of this series was the first phase of a diphasic QRS upward. A small triphasic QRS (only 3 mm. in height) was found once, associated with other electrocardiographic evidence of myocardial damage, viz., notching and slurring of all the leads, an inverted T-wave in Leads I and II, and a negative S-T in Leads I, II and III. In three cases the QRS was monophasic, being exclusively upward. In each of these cases there was other electrocardiographic evidence of myocardial disease, such as a negative T-wave in Leads I or II, slurring and notching of QRS in these leads, "low voltage" (below 5 mm.) in all three leads, or deviations of the S-T segment.

There was no correlation between a deep Q-wave in Lead III (or Leads II and III) and the form of the QRS complex in Lead IV. Nor was there any correlation between the deviation of the electrical axis in the three leads and the form of the QRS complex in Lead IV. Left axis deviation (or left ventricular preponderance) might be associated in Lead IV with a higher positive phase of the diphasic QRS, with a higher negative phase, or with phases of approximately equal magnitude. No instance of right axis deviation was recorded in this series.

T-Wave.—A positive T-wave in Lead IV occurred 16 times. Eleven of these 16 tracings were cases in which the three conventional leads showed changes characteristic of myocardial disease, such as inverted T-waves in I and II, slurring and notching of QRS in I or II, and deviation of the S-T segment. But five of these tracings were from patients whose three-lead electrocardiogram showed no abnormalities. These five patients were as follows: (1) a woman of fifty years with hypertension and an enlarged heart in the roentgenogram; (2) a boy of five years with acute rheumatic fever; (3) a mentally retarded boy of thirteen years with cryptorchidism and with a systolic apical thrill and murmur which may have been due to congenital heart disease or a previously unrecognized attack of acute rheumatic fever; (4) a boy of five years with an indefinite rheumatic history, an

apical systolic murmur, and a globular shaped heart in the roentgenogram; (5) a girl of thirteen years who had had chorea and now presented the evidence of rheumatic heart disease. Patient (1) above, showed a long, flat, low, notched T-wave in Lead IV.

Inasmuch as several of our control tracings showed inverted T-waves of low amplitude (less than 1 mm.) we considered the same finding in our group with cardiac disease to be without significance. There were two cases in which all four leads had T-waves of low amplitude. Otherwise there was no correlation between a low T-wave in Lead IV and low T-waves in the other leads. It is not possible categorically to set the limits of the normal T-wave amplitude—nevertheless, the amplitude of the T-wave in our control group was never less than ½ mm., whereas in those two cases with low amplitude of the T in all leads, T-IV was only ¼ mm. in height.

We found T-IV diphasic ten times; in three of these, the two phases were of equal amplitude; in six others, the negative phase was the larger, and in one, the reverse was true. One of our normals displayed a diphasic T-IV of low voltage (Fig. 1) with the positive phase first. It is possible, that to have significance, a diphasic T-IV must have an amplitude of more than 2 mm., particularly when the major portion of the T-wave is upward. The presence of a diphasic T-IV could not be correlated with any particular feature in the other leads; although there was one case in which the T-wave of all four leads was diphasic. The significance of a diphasic T-IV is uncertain.

We found a deep T-wave in Lead IV four times. Twice there was electrocardiographic evidence of myocardial damage. A negative T-wave, 9 mm. or more in depth, therefore should be viewed with suspicion.

Tentatively, in view of our comparatively small series, we are able to state that the following are abnormal T-waves: (1) a positive T-wave, (2) a diphasic T-wave more than 2 mm. in amplitude and with the positive phase the larger, (3) a shallow, broad negative T-wave with an amplitude of ¼ mm. or less, (4) a deep negative T-wave with an amplitude of 9 mm. or more. Such T-waves in Lead IV are to be considered suggestive of the presence of myocardial damage. They are naturally less significant when they occur alone than when accompanied by other evidence pointing in the same direction.

S-T Segment.—In eight cases there was a positive S-T deviation in Lead IV, a finding not seen in any of the control tracings. Therefore, a deviation of even a half millimeter above the isoelectric line should be viewed with suspicion. Four of the eight tracings showed a positive deviation of 1 mm. or more, and it was precisely these four tracings that were associated with negative or positive deviations of S-T segments of similar magnitude in the conventional leads. The four tracings with positive S-T segments of less than 1 mm. were not accompanied by S-T deviations in the conventional leads.

Two cases presented a negative S-T deviation which we considered significant. In both the deviation was only 1.5 mm. but was associated with a positive T-wave. The three-lead electrocardiogram showed no S-T deviation. Both patients presented marked clinical and electrocardiographic evidence of myocardial disease. Other instances of negative S-T in Lead IV were found, but in no case was the deviation more than 2 mm., and in all the T-wave was negative.

A positive S-T deviation in Lead IV is abnormal when it is more than 0.5 mm. A negative S-T deviation associated with a negative T-wave should exceed 2 mm. to be beyond the normal, and this we have not seen in this group. A smaller negative S-T deviation is abnormal only when the T-wave is positive.

LEAD IV IN RECENT CORONARY OCCLUSION

During the course of this study, we recorded Lead IV in 11 cases of recent coronary occlusion. The 11 sets of tracings fell into three groups: (1) those with changes characteristic of coronary occlusion in Lead IV, (2) those with an abnormal configuration of Lead IV of the type seen in other kinds of heart disease and therefore not specific for coronary occlusion; and (3) those with Lead IV within normal limits. In any one series of records Lead IV might change from the characteristic type of electrocardiogram to the nonspecific abnormal configuration or to normal.

Three types of specific changes were seen. The first, and most common, consisted of a positive S-T segment followed by a negative coronary T-wave which differed little from the normal T-wave. In succeeding records the S-T segment became isoelectric and the T-wave became deeper and then shallower (Fig. 2). The second, seen twice, was the inverted image of the first, consisting of a negative S-T segment followed by positive coronary T-wave such as was recently described in the three-lead electrocardiogram of Bohning and Katz (Figs. 4*A* and 4*B*). The progression of this type was similar to that of the first. The third type, seen three times, was a diphasic T-wave of large magnitude, the first phase of which merged with the descending and sometimes entirely negative S-T segment. The transition between the negative and positive phase was abrupt, making the positive phase sharply peaked (Figs. 3*A* and 3*C*).

In two instances Lead IV of low amplitude was associated with low amplitude of the other leads and minor deviations of the S-T segment in all leads (Fig. 3*B*). This type of tracing, if succeeding records show even slight changes, would tend to substantiate the clinical diagnosis of recent coronary occlusion.

On comparing Lead IV with the three-lead electrocardiogram we found tracings: (1) in which the characteristic changes occurred in all four leads (Figs. 2, 3*A* and 3*B*), (2) in which the characteristic changes occurred only in the three standard leads, and (3) in which the characteristic

changes occurred only in Lead IV (Figs. 3*C*, 4*A*, 4*B* and 4*C*). It is because of this last group that *Lead IV should be taken routinely in all cases of suspected recent coronary occlusion.* This is the plan now followed at the Michael Reese Hospital.

Lead IV varied in appearance in successive tracings when serial records were taken. This is shown in the illustrations. Both the negative and positive coronary T-waves passed through the classical series of changes (Figs.

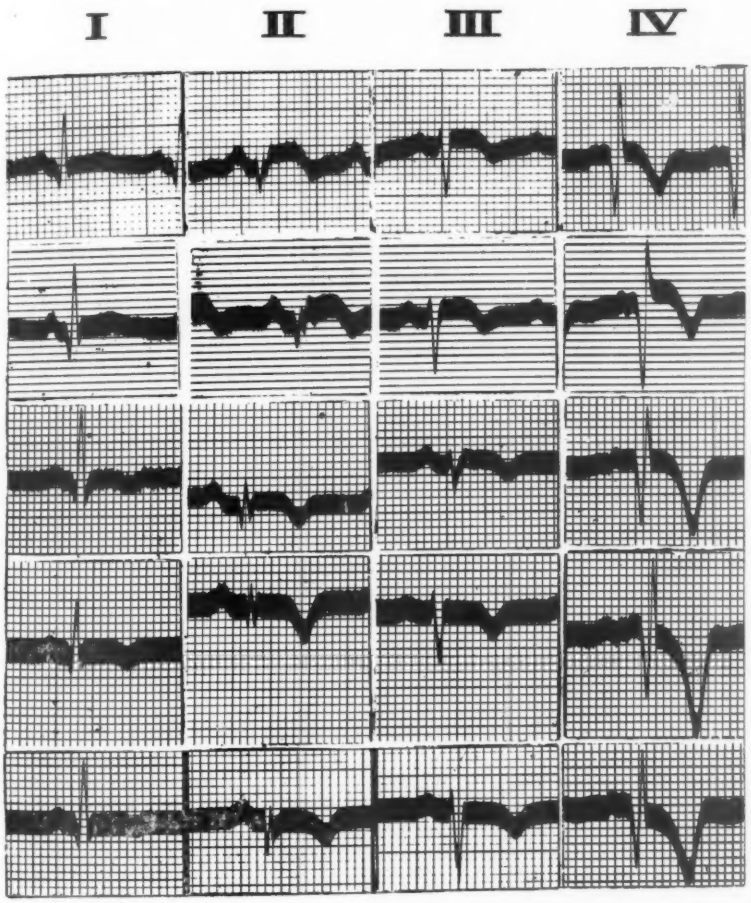

Fig. 2.—Serial electrocardiograms from a case of coronary occlusion. Note the S-T deviation in Leads II, III and IV. The T-wave passes through characteristic changes in all leads.

2, 4*B*, and 4*C*); although in one case, with almost monophasic ventricular deflections in the standard leads, the negative T-wave became diphasic in a later record, and the positive S-T segment became negative (Fig. 3*A*). In one case a diphasic T-wave became negative in a later record (Fig. 3*C*). Quite frequently Lead IV appeared normal at one stage. In several instances QRS became monophasic and positive.

The progression of the changes in Lead IV did not always parallel those in the ordinary leads. Sometimes Lead IV changed less rapidly than the other leads, but usually the reverse was true. Occasionally all leads progressed in parallel fashion.

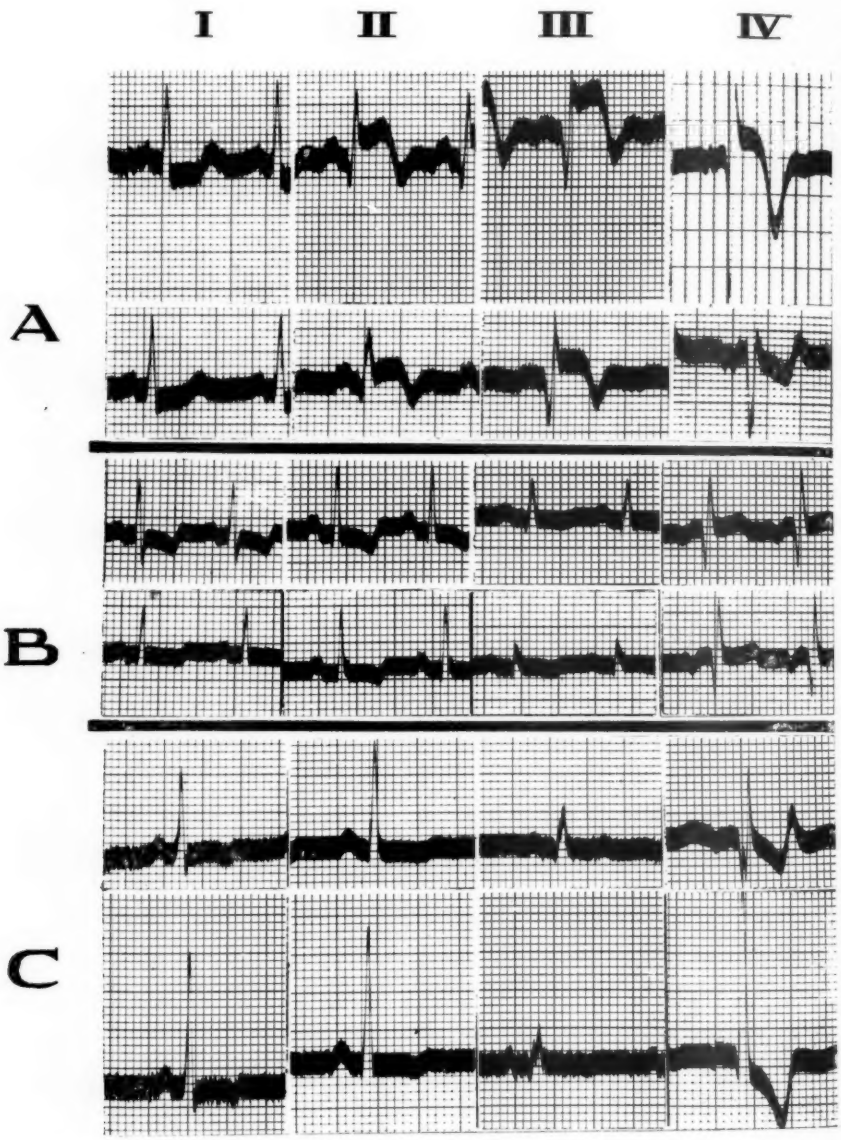

Fig. 3.—Serial electrocardiograms from three cases of coronary occlusion. Note in *A* and *B* changes in all four leads; in *C* changes only in Lead IV. Note in *B* low "voltage" in all four leads.

While it is true that Lead IV helps to explore the heart currents more thoroughly and that with it fewer cases of coronary occlusion will be missed

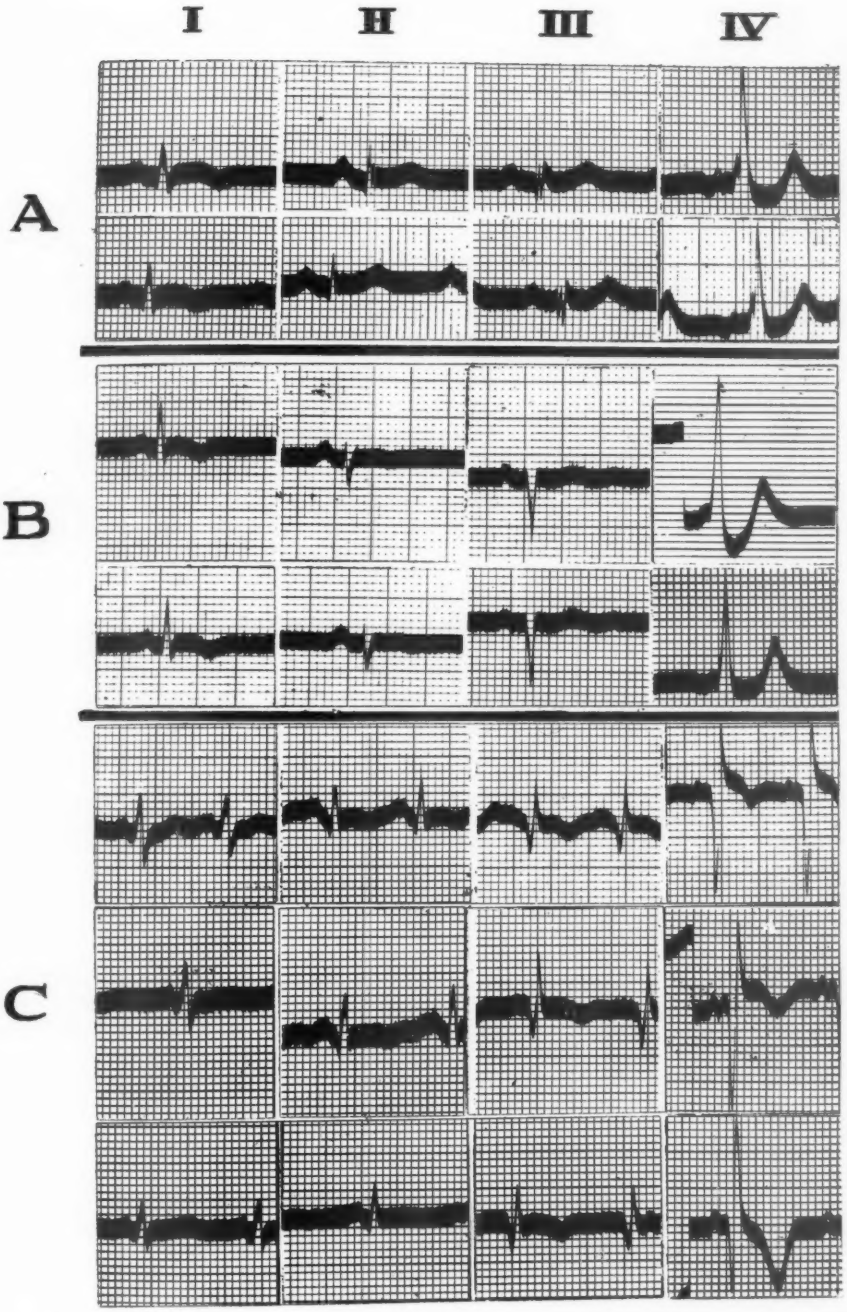

Fig. 4.—Serial electrocardiograms from three cases of coronary occlusion showing characteristic changes only in Lead IV. Contrast the large amplitude of the QRS complex in Lead IV of *A* with the low amplitude of the QRS complex in Lead IV of Fig. 3*B*, although the three-lead electrocardiogram in both instances is of low amplitude.

with the electrocardiogram, it is too early to hope that this lead will aid in the localization of the site of infarction, as Wolferth and Wood[1] anticipated.

SUMMARY

1. Lead IV (Wolferth and Wood[1]) normally has an inverted or diphasic P-wave, a diphasic QRS, the first phase of which is inverted, and an inverted T-wave resembling superficially the negative coronary T-wave. The characteristics and limits of normal in our 25 cases are discussed in detail.

2. The time relationships of the deflections of Lead IV are the same as those in the other leads.

3. Lead IV can separate those cases in which low amplitude in the three-lead electrocardiogram is caused by change in the heart's position from those due to intraventricular block or increased body shunting.

4. Noticeable slurring and notching of QRS in Lead IV is to be regarded as abnormal and should be considered in the same light as slurring or notching in Leads I or II. There is no constant change in Lead IV in left axis deviation shift or left ventricular preponderance. A monophasic QRS in Lead IV indicates myocardial damage.

5. The following are abnormal T-waves in Lead IV and suggest myocardial damage: (a) a positive T-wave, (b) a diphasic T-wave, taller than 2 mm. and with the positive phase the larger, (c) a shallow broad negative T-wave less than ¼ mm. high, (d) a negative T-wave deeper than 9 mm.

6. A positive S-T segment, a negative S-T segment of more than 2 mm., or any negative S-T deviation when associated with a positive T-wave are indicative of myocardial involvement.

7. The presence of any one of the abnormalities in Lead IV described above are to be considered in the same way as abnormalities of the QRS complex, S-T segment and T-wave of the ordinary leads. They are less significant when they occur alone than when accompanied by other electrocardiographic evidence pointing in the same direction.

8. Three types of changes occurring in Lead IV are "specific" for recent coronary occlusion: (a) a positive "humped" S-T segment with a negative coronary T-wave, (b) a negative "humped" S-T segment with a positive coronary T-wave, (c) a diphasic coronary T-wave which is transient. The first two types pass through the usual sequence in a series of records described for other leads. The progression of changes in Lead IV in a series of records is not always parallel to that in the ordinary leads. Often the changes progress most rapidly in Lead IV.

9. While Lead IV may show no abnormalities, or only nonspecific types of abnormalities in recent coronary occlusion, there are in the five cases reported by Wolferth and Wood[1, 2] and the 11 reported by us, a sufficient

number of cases (7 out of 16) in which the specific changes occurred only in Lead IV. *Therefore, Lead IV should be taken routinely in all cases of suspected recent coronary occlusion.*

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THE ETIOLOGY OF HEART DISEASE IN WHITES AND NEGROES IN TENNESSEE*

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THE diagnosis of "heart disease" does not convey an idea of the nature of the disease process, because the underlying etiology varies and is sometimes multiple. Obviously, the first step in the development of a program of prevention of heart disease is the acquirement of knowledge of the etiological factors involved. These factors have been found to vary with the geographical location, race, climate, and mode of life.

Studies of large groups of patients with heart disease from the point of view of etiology have been reported in this country by White and Jones,[6] Wood, Jones, and Kimbrough,[8] Davison and Thoroughman,[2] Coffen,[1] Stone and Vanzant,[4] Viko,[5] Schwab and Schulze,[3] and others. Such studies have a twofold value; they add to the accumulated data concerning the etiology of heart disease, and they also enable local groups to visualize their particular problems. The study reported here was initiated with these two objectives.

The patients studied were those admitted to the wards and out-patient department of the Vanderbilt University Hospital during the calendar years 1930 and 1931. This group includes both whites and negroes and represents diverse economic levels. A study of such a series, therefore, not only affords information concerning the incidence and etiology of heart disease in the general population of Tennessee but also offers an opportunity to compare these findings in the white and negro races.

During the two-year period 16,935 new patients were admitted to the various divisions of the out-patient department and the hospital. Of this number 11,198 (66.2 per cent) were whites and 5,737 (33.8 per cent) were negroes. This ratio closely approximates the racial percentages in the vicinity of Nashville. From these patients were selected all those who exhibited definite objective evidence of heart disease. These numbered 645, and each of them showed one or more of the following evidences of cardiac disease: unequivocal cardiac enlargement, congestive heart failure, mitral stenosis, aortic insufficiency and/or stenosis, congenital abnormality, auricular fibrillation, auricular flutter, heart-block (electrocardiographic evidence), coronary occlusion, angina

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pectoris, pericarditis (acute or chronic), bacterial endocarditis, aneurysm of the aorta.

The records of these 645 cases were then subjected to analysis. Each record included a history, a physical examination, and the results of Wassermann test, urinalysis, and other indicated laboratory procedures. Cardiac measurements were verified by teleroentgenogram in 434 (67.4 per cent) and electrocardiographic tracings made in 362 (56.2 per cent) of the patients. One hundred and sixteen of these 645 died during the two-year period and 71 autopsies were obtained. In only one case was the pre-mortem diagnosis of *etiology* altered by the post-mortem examination. On the basis of all available information each patient was classified etiologically, or placed in the "unclassified" group if adequate evidence was lacking. The classification used and the criteria for the classification are the ones proposed by White and Myers,[7] with certain modifications, which consist mainly of a consolidation of the hypertensive and arteriosclerotic groups of heart disease. We found it impossible to separate these groups of cases with any degree of accuracy. A large percentage of these who showed definite arteriosclerosis had hypertension, and some of those with arteriosclerosis and cardiac hypertrophy who did not have an elevated blood pressure when observed may well have had it in the past. In each instance of mixed etiology, if there was not an etiological factor which was clearly dominant, the case was grouped with those of doubtful or unknown etiology under the heading "Unclassified." The number so placed was small and does not serve to alter appreciably the percentages in the other groups.

RESULTS

I. Incidence.—Table I reflects the incidence of organic heart disease among the 16,935 patients admitted. The total incidence of 3.8 per cent is of less significance than the difference in the incidence in the two race groups. Four and nine-tenths per cent of the negroes seen but only 3.3 per cent of the whites had heart disease.

TABLE I

INCIDENCE OF ORGANIC HEART DISEASE IN 16,935 PATIENTS

Patients Admitted to Wards and Out-Patient Department			Percentage of total
White	11,198		66.2
Negro	5,737		33.8
Total	16,935		100.0
Organic Heart Disease Among the Group		**Percentage of racial group**	
White	365	3.3	
Negro	280	4.9	
Total	645		3.8

II. Occurrence of Etiological Types.—In Table II are summarized the etiological factors in our 645 cases of heart disease and their relation to age groups and race. In general these data indicate that arteriosclerotic-hypertensive disease (67.9 per cent), the rheumatic fever complex (10.5 per cent), and syphilis (7.9 per cent), together cause 86.3 per cent of the heart disease observed in the Vanderbilt University Hospital. They also emphasize that while heart disease due to arteriosclerosis and hypertension occurs with almost equal frequency in the white and negro races, rheumatic heart disease assumes a frequency in the white race similar to the frequency of syphilitic heart disease in the negro. This last point is borne out by the figures collected (in Table III) from various clinics having the opportunity to compare large groups of white and negro patients.

a. Arteriosclerotic-Hypertensive Heart Disease. This group includes 438 patients (67.9 per cent of the series). It is thus numerically much the most important group. This type of heart disease affects 71.8 per cent of the negro patients and 65.1 per cent of the white. The most constant physical finding in this group is cardiac hypertrophy, which was present in 95.9 per cent of our cases. In 59.2 per cent of the 438 patients, teleroentgenograms were made. Electrocardiograms in 226 cases revealed auricular fibrillation in 28 (6.4 per cent of the group), bundle-branch block in 15 (3.4 per cent), and signs usually ascribed to coronary occlusion in 5 (1.1 per cent). All the 19 cases of angina pectoris which were seen during the period under review had definite evidence of arteriosclerotic-hypertensive heart disease, and have been included under this classification. Although 201 negroes are in this etiological group, only 3 of them had angina pectoris. Ninety-six (21.9 per cent) of the patients in this group were at least 20 per cent overweight.

b. Rheumatic Heart Disease. This group of 68 patients (10.5 per cent of the series) includes 15.3 per cent of the cases of heart disease in the white race and only 4.3 per cent of the cases in the negroes. The valves involved were as follows:

Mitral alone	44
Aortic alone	3
Mitral and aortic	21

In no instance was the diagnosis of adhesive pericarditis made. Electrocardiograms of 52 of the cases revealed: auricular fibrillation in eight instances, varying degrees of heart-block in three, and nodal rhythm in two.

c. Syphilitic Heart Disease. Of the 51 patients (7.9 per cent of the series) who had syphilitic heart disease, 43 were negroes. This type of heart disease accounted for 15.4 per cent of the negro cases, exactly seven times the frequency with which it was encountered in whites

TABLE II

ANALYSIS OF 645 CASES OF ORGANIC HEART DISEASE

ETIOLOGY		AGE GROUPS 0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	MALE	FEMALE	TOTAL	PERCENTAGE RACIAL	PERCENTAGE OF TOTAL
Arteriosclerosis and hypertension	White	1	1	3	10	36	71	69	39	7	148	89	237	65.1	
	Negro			5	27	46	70	40	12	1	89	112	201	71.8	
	Total	1	1	8	37	82	141	109	51	8	237	201	438		67.9
Rheumatic infection	White	4	18	17	11	4	2				23	33	56	15.3	
	Negro		1	6	4		1				6	6	12	4.3	
	Total	4	19	23	15	4	3				29	39	68		10.5
Syphilis	White				2	2	3	1			6	2	8	2.2	
	Negro			2	14	12	13	2			37	6	43	15.4	
	Total			2	16	14	16	3			43	8	51		7.9
Congenital defect	White	7	3	4			1				10	5	15	4.1	
	Negro	1	3	2							5	1	6	2.1	
	Total	8	6	6			1				15	6	21		3.3
Bacterial endocarditis	White		1	1	3		2	3			6	4	10	2.7	
	Negro						1				1		1	0.4	
	Total		1	1	3		3	3			7	4	11		1.7
Diphtheria	White	8									4	4	8	2.2	1.2
Thyrotoxicosis	White			2	1		1				1	3	4	1.1	
	Negro					1	2					3	3	1.1	
	Total			2	1	1	3				1	6	7		1.1
Chronic pulmonary disease	White					2		1			2	1	3	0.8	
	Negro				1	1					2		2	0.7	
	Total				1	3		1			4	1	5		0.8
Trauma	Negro			2							2		2	0.7	0.3
Miscellaneous infections	White	1	1	1	1	3	2	1			8	2	10	2.7	
	Negro			2	1		1				3	1	4	1.4	
	Total	1	1	3	2	3	3	1			11	3	14		2.2
Unclassified	White	1	2	4	1	3	1	2			8	6	14	3.8	
	Negro			1	3	2					2	4	6	2.1	
	Total	1	2	5	4	5	1	2			10	10	20		3.1
Total	White	22	26	32	29	50	83	77	39	7	216	149	365	100.0	
	Negro	1	4	20	50	62	88	42	12	1	149	131	280	100.0	
	Total	23	30	52	79	112	171	119	51	8	365	280	645		100.0

TABLE III

COMPARATIVE STATISTICS ON THE ETIOLOGY OF HEART DISEASE IN THE SOUTH

	TEXAS[4]		GEORGIA[2]	VIRGINIA[8]		TEXAS[3]		TENNESSEE*		TOTAL	
NO. OF PATIENTS	WHITE 501	NEGRO 414	NEGRO 257	WHITE 188	NEGRO 112	WHITE 488	NEGRO 1,172	WHITE 365	NEGRO 280	WHITE 1,542	NEGRO 2,235
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Arteriosclerotic and hypertensive	65.0	56.8	61.3	59.0	60.7	78.3	76.8	65.1	71.8	66.9	65.6
Rheumatic	10.4	3.6	7.2	28.3	11.6	7.4	1.8	15.3	4.3	15.4	5.7
Syphilitic	9.2	31.7	25.3	4.7	21.4	6.8	15.3	2.2	15.4	5.8	21.8
Congenital	1.0	0.2	0.8	1.5	—	0.6	0.8	4.1	2.1	1.8	0.8
Thyrotoxic	1.4	1.2	—	3.9	3.6	2.9	2.3	1.1	1.1	2.4	1.6
Subacute bacterial endocarditis	1 8	1.2	1.2	—	—	—	—	2.7	0.4	1.1	0.5
Miscellaneous	1.4	1.2	—	0.5	—	1.5	0.7	2.7	1.4	2.0	0.9
Unclassified	5.6	4.1	4.2	2.1	2.7	2.5	2.3	3.8	2.1	3.5	3.1
Angina pectoris	4.2	—	—	—	—	—	—	—	—	1.1	

*Present report.

(2.2 per cent). The marked preponderance of syphilitic heart disease in males of both races bears out previous studies.[2, 3, 4, 6, 8] The cardiac lesions were as follows:

Aortic insufficiency	30	58.8 per cent
Aortic insufficiency and aneurysm	10	19.6 per cent
Aneurysm alone	8	15.7 per cent
Myocardial lesions	3	5.9 per cent

Electrocardiograms in thirty cases revealed two with bundle-branch block.

The presence of arteriosclerosis and systolic hypertension among this group was a frequent finding as shown below:

Hypertension and arteriosclerosis	21
Hypertension without manifest arteriosclerosis	11
Arteriosclerosis without hypertension	3
No hypertension or arteriosclerosis	16
	51

A systolic hypertension was observed in thirty-two of the fifty-one patients in this group, but in only eight of these thirty-two cases with hypertension was the diastolic pressure above 90. These eight undoubtedly represent a mixed type of etiology with the hypertension playing a rôle in the disability, but from careful study of the patients the principal cardiac damage can be attributed to the luetic infection.

Substernal pain was a frequent symptom in the patients of this group, but not one of them gave a history typical of angina pectoris.

d. Miscellaneous Types of Heart Disease. The remaining types of heart disease were so limited in number as to furnish little of statistical interest, aside from their ratio to the total number of cases of heart disease.

III. Racial Comparison.—The data in Table III, a summary of 2,235 cases of heart disease in the negro and 1,542 cases in the white race, are all drawn from published statistics collected in southern hospitals and dispensaries. The first group was compiled by Stone and Vanzant from patients seen in Galveston, Texas; the second by Davison and Thoroughman in Atlanta, Georgia; the third by Wood et al. in Richmond, Virginia; the fourth by Schwab and Schulze in Galveston, Texas; the fifth is our series. The criteria for diagnosis were essentially the same in all.

It is at once apparent that in the negro race the two main causes of heart disease are arteriosclerosis-hypertension and syphilis. Both of these processes are primarily vascular, so that it appears reasonable to suppose that the vascular system of the negro is susceptible to attack by disease processes.

In addition to the differences in the incidence of etiological factors in the two races, the negro develops heart disease at an earlier age,

on the average, than the white. Fig. 1 shows graphically the abrupt rise in the incidence of arteriosclerotic hypertensive heart disease in successive age groups in the negro race as compared with the more gradual ascent and decline in the white race. Stone and Vanzant[4] have prepared a similar chart in their study, and the difference is even more striking. Likewise, in the incidence of syphilitic heart disease, the negro race shows a tendency to reach a peak at least a decade before the white race. It is true that the number of white patients with syphilitic heart disease in our series is too small to furnish comparable statistics, but analyses by White and Jones[6] and Viko[5] of syphilitic heart disease in their communities furnish figures which may be compared with our studies of the negro, and bear out this contention.

Angina pectoris is rare in our negro patients. Substernal pain is not an uncommon complaint with them, but the typical attacks of paroxysmal pain so characteristic of angina pectoris are seldom found.

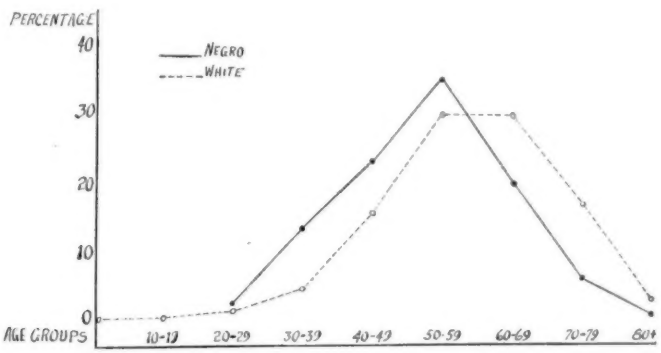

Fig. 1.—Arteriosclerotic hypertensive heart disease, age incidence.

Rheumatic fever, subacute bacterial endocarditis, and miscellaneous infectious processes are much less common causes of heart disease in the negro. The statistics furnished in Table III indicate that such types of heart disease are at least two or three times as common in the white race.

It is apparent that heart disease in the South differs somewhat in etiology from heart disease in other parts of the United States. The large negro population, with its increased incidence of syphilitic heart disease, and the comparative infrequency of the rheumatic infection make our approach to the preventive program somewhat different from that advisable in other sections. The greatest single cause, arteriosclerosis-hypertension, remains, however, as a universal problem.

SUMMARY AND CONCLUSIONS

1. Six hundred forty-five cases of organic heart disease were studied with reference to etiology, racial distribution, sex, and age.

2. Organic heart disease occurred in 4.9 per cent of all negroes coming to the Vanderbilt University Hospital and Out-Patient Department in 1930 and 1931, and in 3.3 per cent of the whites. The incidence in the negro race was therefore 1.5 times greater than in the white race.

3. Arteriosclerotic hypertensive heart disease accounted for 65.1 per cent of the cases in the white race and 71.8 per cent in the negro race. Rheumatic heart disease formed 15.3 per cent of the cases in the whites and only 4.3 per cent in the negroes, while syphilitic heart disease was seven times more common in the negro than in the white, 15.4 per cent and 2.2 per cent respectively.

4. Comparative statistics from various sources show that the etiology of heart disease varies somewhat in different sections of the United States. Therefore, the problems of the prevention of heart disease are not identical in all parts of the United States.

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THE SILHOUETTE OF THE HEART AND THE AORTIC ARCH

Orthodiagraphic Measurements

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TRANSVERSE DIAMETER

TO ESTIMATE the size of the human heart various measurements have been suggested; principally, the transverse diameter of the frontal plane at its widest points, the combination of different diameters and the surface area of the frontal plane. The transverse diameter is the measurement most commonly employed. It is practicable because it can be obtained in a few seconds, requiring only ordinary care and no special skill. It can be accurately measured only by orthodiagraphy.

The validity of the transverse diameter as an index of the heart's size is attested by the work of Bardeen,[1] of Hodges and Eyster,[2] of Bedford and Treadgold,[3] of Treadgold and Burton,[4] and by my own work.[5]

Standards.—Inasmuch as normal hearts vary considerably in size, such a measurement will have value if it can be established that it is not haphazard, but that it bears a constant relation to some standard which is adjustable to normal variations of size. Several standards, all based on the physical characteristics of human beings, have been proposed for estimating or predicting what the transverse diameter of the heart should be in any normal individual.

In a previous paper[5] the accuracy of Hodges and Eyster's prediction formula[2] and that of cardiothoracic ratio[7] were tested by comparing the actual diameters obtained by orthodiagrams with the estimated normal diameters in 100 "noncardiac" males and 75 "noncardiac" females. For females an adjusted standard which is 0.8 cm. smaller than the male prediction figure was used.

Standards based on weight, on body surface area and on height are now added. To obtain the weight standard the subjects were arranged in groups, each group comprising individuals weighing within 5 kilograms of each other. The average transverse diameter for a group was used as a standard, and the difference between this figure and the actual transverse diameter of each individual heart in the group was considered the variation from the standard or predicted diameter for that case. This is the method used by Treadgold and his associates.[3, 4] To obtain the body surface area standard, a similar plan used by

Kissane[6] was adopted, taking 0.1 square meter as the range of measurement for each group. Individuals within 2.0 cm. of each other formed the groups for getting the height standard.

Table I presents the comparative merits of each prediction method by showing the percentage of cases whose actual transverse measurements are within 0.5 cm. of the predicted diameter, of those within 1.0 cm., and also the percentage of those that are wider by more than 1.0 cm. In the last column the average variation of the actual from the predicted diameter is recorded. The 100 normal male hearts are used in making the comparison.

TABLE I

THE ACTUAL TRANSVERSE DIAMETER

	WITHIN ± 0.5 CM. OF THE PREDICTED DIAMETER PER CENT	WITHIN ± 1.0 CM. OF THE PREDICTED DIAMETER PER CENT	LARGER BY MORE THAN 1.0 CM. PER CENT	AVERAGE VARIATION CM.
Hodges and Eyster formula	61	85	6	0.53
Weight	51	86	10	0.61
Body surface area	47	72	13	0.73
Height	34	61	20	0.94
Cardiothoracic ratio	28	60	17	1.00

The figures in this table indicate that while the formula of Hodges and Eyster is not perfect, it is a better criterion than any of the others. According to the average variations found it is superior to the weight standard by 15 per cent, to the standard based on body surface area by 37 per cent, to the height standard by 77 per cent and to the cardiothoracic ratio by 90 per cent. Treadgold and his associates acknowledge the superiority of Hodges and Eyster's formula, but consider the weight standard as used by them a satisfactory guide for clinical purposes. They seek to improve the weight standard by adding to the estimated transverse diameter when the weight of an individual is above the average for his physique and by subtracting from it when the height is above the average. This is the fundamental principle of Hodges and Eyster's formula wherein the predicted diameter is directly proportionate to weight and inversely proportionate to height. My own data on the actual diameter in both male and female hearts are generally in accord with this principle.

If the transverse diameter of a normal heart is directly proportionate to weight and inversely proportionate to height, then it follows that a prediction figure based on body surface area is untenable as a standard because body surface area is directly proportionate to both height and weight. The comparative figures in Table I substantiate this conclusion.

It is rather surprising that the cardiothoracic ratio which has been so universally employed as a guide in judging the size of the heart should prove to be the poorest standard of all those considered.

Enlargement.—Hodges and Eyster concluded that the chances are three to one in favor of pathological increase in size of the heart when the transverse diameter is wider than the predicted diameter by more than 0.5 cm. Eyster evidently considered such a limitation of the normal too narrow, for he later[8] expressed the opinion that a heart was enlarged when its transverse diameter exceeded the predicted diameter by more than 10 per cent. This conclusion apparently is based on data from two series, each 100 normal cases, in the first[9] of which only three hearts exceeded this measurement and in the second[8] only eight hearts. In only 5.5 per cent of 200 normal cases, therefore, did the transverse diameter exceed the predicted diameter by more than 10 per cent. Bedford and Treadgold[3] submitting a group of 116 normal cases to Hodges and Eyster's formula found only 4.3 per cent with an increase of more than 10 per cent.

In my own series of 175 cases[5] the actual increase in size instead of the percentage was used. Seven cases or 4 per cent had a transverse diameter wider than the predicted diameter by more than 1.0 cm. There is no difference between 1.0 cm. increase and 10 per cent increase in a heart whose transverse diameter is 10.0 cm., and in a heart of average size the difference is too small to be of any practical importance in ordinary clinical work.

As a result of these separate orthodiagraphic studies on the transverse diameter of 491 normal hearts, one is in a position to establish a line of demarcation between normal and enlarged hearts. Twenty-three hearts, or a little less than 5 per cent, had a transverse diameter either 10 per cent or 1.0 cm. wider than the predicted diameter, and it is therefore fair to conclude that when a heart is found with this degree of increased size the chances are over 95 per cent in favor of such a heart being pathologically enlarged.

As a definition of enlargement this criterion applies only to hearts previously normal in size, because an abnormally small heart may increase considerably in volume before its transverse diameter is 1.0 cm. larger than the predicted figure.

Table II presents an arrangement showing the variation of the actual transverse diameter from the predicted diameter according to formula of Hodges and Eyster in 175 normal individuals contrasted with 471 abnormal cases, the latter being divided as follows: 44 with functional disturbance but with no evidence of structural change, 70 in whom the diagnosis was uncertain and therefore called possible heart disease[10] and 357 with organic heart disease.

The measurements of 84 cases of the total 646 have been omitted from the table because the transverse diameter was smaller than the predicted diameter by more than 0.5 cm. They are divided as follows: normal 41, noncardiac with functional disturbance 8, possible heart disease 12, and pathological group 23. All subjects were ambulatory.

TABLE II

THE ACTUAL TRANSVERSE DIAMETER

		WITHIN ± 0.5 CM. OF PREDICTED DIAMETER		WIDER THAN PREDICTED DIAMETER BY MORE THAN 0.5 CM. BUT LESS THAN 1.0 CM.		WIDER THAN THE PREDICTED DIAMETER BY MORE THAN 1.0 CM.	
	CASES	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Normal	175	106	60.5	21	12	7	4
Noncardiac with function disturbance	44	28	63.5	6	13.6	8	4.5
Possible heart disease	70	27	38.5	15	21	16	23
Pathological	357						
1. Thyrotoxic	11	5	45	2	18	3	27
2. Hypothyroid	2	0	0	0	0	2	100
3. Cardiac insufficiency	12	1	8	1	8	9	75
4. Mitral stenosis	39	11	28	11	28	14	36
5. Mitral stenosis and insufficiency	29	4	14	0	0	24	83
6. Mitral insufficiency	27	6	22	4	15	16	54
7. Mitral and aortic disease	34	1	3	2	6	31	91
8. Luetic Aortitis	9	1	11	2	22	6	66
9. Coronary sclerosis without hypertension	51	17	33	9	1.7	17	33
10. Coronary sclerosis with hypertension	45	17	38	4	9	24	53
11. Sclerosis of aorta with hypertension	33	2	6	5	15	24	73
12. Sclerosis of aorta without hypertension	13	4	30	2	15	6	46
13. Essential hypertension	52	14	27	10	20	23	44
Total Pathological group		83	23	52	14	199	56

It is generally recognized that heart disease does not always cause manifest enlargement of the heart. Table II indicates that this is frequently so, 27 to 45 per cent in such conditions as thyrotoxicosis, mitral stenosis, coronary sclerosis, both with and without hypertension, and essential hypertension. There are certain factors, however, which must be considered in the interpretation of these figures. In many of the pathological cases the absence of increased size may be more apparent than real. For purposes of this study hypertension was considered present when the blood pressure was over 140/90 mm.,[12] or when the systolic pressure was over 150 mm. regardless of the diastolic pressure,

or the diastolic pressure over 100 mm. regardless of the systolic pressure. Using this criterion no cases of hypertension could escape detection, but at the same time some patients, seen but once, may have had only a temporary rise of pressure due to the excitement of the examination. It is possible that this condition may account partly for the normal range in size in some cases of hypertension.

It is also possible that a few of these pathological hearts may have been unduly small before the advent of disease and as a result of disease may have increased considerably in size and still be included within the confines of the normal or borderline measurements. For example, a heart which in health was 1.0 cm. smaller than the normal range would have to increase its transverse diameter by more than 2 cm. before it could be included in the group of large hearts. Fortunately changes in contour often will indicate that there is enlargement of the heart or of some of its chambers regardless of the actual measurements. However, this study has been concerned not with enlargement as such, but only with the significance of size in hearts whose transverse diameter is larger than the predicted by more than 1.0 cm.

With these reservations in mind it is reasonable to expect that in any mixed group of pathological cases 56 per cent of the hearts will be found enlarged as against 4 per cent of the normal cases, while 44 per cent will not show that increased size as against 96 per cent of normals. The 44 noncardiac patients with functional disturbances, but with no evidence of structural disease, have hearts with approximately the same measurements as normal individuals, an agreement which is consistent with the diagnosis. In Class E (possible heart disease) 23 per cent of hearts are in the large group, as against 4 per cent of normal hearts and 56 per cent of pathological hearts, indicating some justification for the unsatisfactory designation of possible heart disease.

WIDTH OF AORTIC ARCH

The frontal plane of the so-called base of the heart forms a shadow under the x-ray which includes the ascending aorta and arch, the pulmonary artery and at times the first part of the descending aorta. The outline is usually delineated with ease in an orthodiagram from which exact measurements can be made. Such measurements have a limited value, but may be useful in providing information about the variations in size in that part of the silhouette which is produced by the ascending aorta and arch. For this purpose one of three different measurements has been employed.

One measurement near the top of the arch is made from the farthest point on the left of the aortic knob to the farthest point on the right at which the aortic shadow is visible at this level (*b* and *c* in Fig. 2). Aside from the difficulty of visualizing the right border of the aorta at this

level because it is so frequently hidden by the bony shadows of the sternum and vertebral column, this measurement has a doubtful value. It represents the base of a curve formed merely by a segment of the

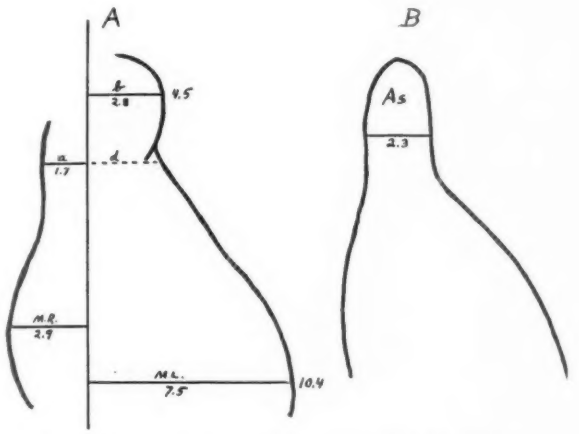

Fig. 1.—Normal female, aged twenty-five years, weight 57 kilo., height 154 cm. *A*, Orthodiagram, anteroposterior position: TD 10.4 cm., (predicted TD 10.6 cm.); width of aortic arch $(a+b)$ 4.5 cm., (average normal width 4.6 cm.); width of great vessels $a+d$.

B, Orthodiagram, right oblique position; diameter of ascending aorta (*As*) 2.3 cm.

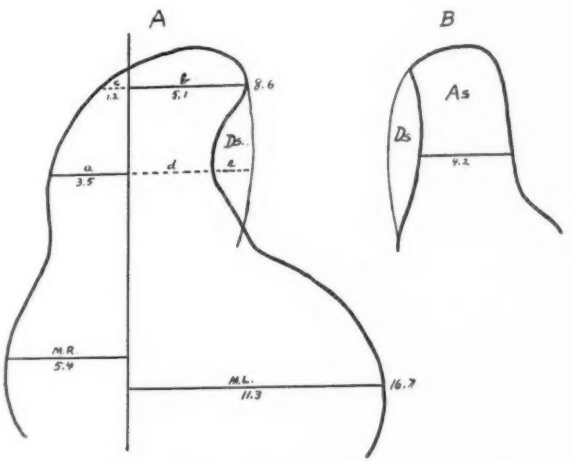

Fig. 2.—Male, aged fifty-five years, weight 84 kilo., height 175 cm. Diagnosis arteriosclerosis and hypertensive heart disease.

A, Orthodiagram, anteroposterior position; TD 16.7 cm. (Predicted TD 13.5.); width of aortic arch $(a+b)$ 8.6 cm. (average normal width 6.1 cm.); line of measurement near upper border of arch, $b+c$; width of great vessels $a+d+e$; *Ds*, descending aorta.

B, Orthodiagram, right oblique position: Diameter of ascending aorta (*As*) 4.2 cm.; *Ds*, descending aorta.

arch. If the ascending aorta passes diagonally beneath the sternum, the measurement will be much smaller than if the course of the vessel is more vertical. This is seen in Fig. 2*A* where there is considerable in-

crease in the width of the shadow produced by the ascending aorta and arch, while the measurement of $b + c$ which is 6.3 cm. would indicate that the size of the silhouette is normal.

A second measurement is called the diameter or width of the great vessels. In Figs. 1*A* and 2*A* this is represented by the lines *a* and *d*, the shadow being produced by the ascending aorta and pulmonary artery which lie side by side at this point. The shadow cannot be separated into the two component parts, and, if there be increase in size, it is impossible to tell from this measurement whether an abnormality in the aorta or pulmonary artery is responsible for the enlargement. In Fig. 2*A* the line *a*, *d* and *e* represents the width of the same two vessels in addition to that part of the descending aorta which can be visualized. Lying in a deeper vertical plane the silhouette of the descending aorta is easily identified. It is usually seen only when there is tortuosity or dilatation of the descending aorta, but inasmuch as the complete width of the vessel is never visualized in this position, any measurement of the shadow is quite valueless.

The measurement chosen for this study is that suggested by Vaquez and Bordet[11] which they call the transverse diameter of the arch. Measurement is made from the midsternal line to the farthest point on the right of the ascending aorta and to the farthest point on the left of the aortic knob (*a* and *b* in Figs. 1 and 2). The sum of these two measurements represents the width of the aortic arch. It is actually the base of an arc formed by the outer margins of the shadows of the ascending aorta and arch.

In making an orthodiagram of the width of the aortic arch care must be exercised to differentiate the ascending aorta from the superior vena cava. The former almost always shows a border which is more or less convex, the latter a border which is straight in the lower part and usually slightly concave in the upper part. Occasionally the ascending aorta is completely hidden by the bony shadows of the sternum and vertebral column.

This measurement of the basal silhouette is not a measurement of any one structure. It is really an index of the size of the curve produced by the shadows of the ascending aorta and arch and has a value only if it can be shown that it is fairly constant in normal individuals and is subject to change in dimensions under the influence of abnormal conditions of the vessel.

Table III presents the measurements obtained from normal individuals.

Table III shows the average width of the aortic arch in 178 adults according to sex and age. The figures of Vaquez and Bordet[11] are added for comparison. The table indicates that the shadow has a wider

TABLE III

WIDTH OF AORTIC ARCH

AGES	CASES	AVERAGE WIDTH	EXTREMES	VAQUEZ AND BORDET
		CM.		CM.
NORMAL MALES				
17-19	9	4.6	4.0 to 5.0	4 to 5
20-29	24	5.2	4.2 to 6.6	5
30-39	21	5.5	4.3 to 6.4	5 to 6
40-49	25	5.7	4.8 to 6.7	5.5 to 7
50-59	14	6.1	4.7 to 7.0	6 to 7
	93			
NORMAL FEMALES				
16-19	11	4.3	3.8 to 5.2	
20-29	31	4.6	3.9 to 5.5	
30-39	24	5.0	4.0 to 6.2	
40-49	13	5.1	4.4 to 5.7	
50-59	6	5.6	5.1 to 6.1	
	85			

measurement in men than in women and that its size gradually increases with age.

Table IV shows the number and percentage of these normal cases having a width of the arch within 0.5 cm. of the average measurement and also the number and percentage of those whose measurement exceeded the average by more than 0.5 cm.

TABLE IV

VARIATION FROM THE AVERAGE AORTIC ARCH WIDTH

	WITHIN 0.5 CM. OF AVERAGE WIDTH		MORE THAN 0.5 CM. GREATER THAN AVERAGE WIDTH	
	CASES	PER CENT	CASES	PER CENT
Normal males 93 cases	71	76	11	12
Normal females 85 cases	67	78	12	14
Total 178	138	77	23	13

According to this table in 77 per cent of these cases the width of the aortic arch was within 0.5 cm. of the average width for each group according to sex and age. In 13 per cent the width of the arch was greater than the average by over 0.5 cm. The remaining 10 per cent were smaller by more than 0.5 cm. and are not tabulated.

It is to be expected that there will be an increase in the width of the arch in a short heavy individual who has a high diaphragm which tends to push both the heart and the aorta upward. Displacement of this kind will cause a wider sweep in the curve of the first part of the aorta and therefore a greater measurement without a necessary change in the caliber of the vessel. Of the 23 cases with the increased width

of more than 0.5 cm. 14 were appreciably overweight and 10 of these were short in stature.

Inasmuch as only 13 per cent of normal subjects show a measurement of the shadow of the aortic arch which exceeds the average for the group according to sex and age by more than 0.5 cm., it seems fair to conclude that 87 per cent of individuals presenting this degree of increase in size have an enlargement of the silhouette which is due to pathological change. If the short thick-set individuals could be excluded, the prediction figure would be improved.

It would be rather premature to suggest that these figures establish a standard. The final value of such data and the validity of the conclusions may be determined by the examination of a larger number of normal controls and by comparison with groups of pathological cases.

An interesting comparison is made with a group of patients having mitral valve disease, a condition in which one does not expect to find any structural change in the aorta. Ninety-five such patients were examined. In 21 cases the measurement could not be made either because the ascending aorta was obscured or because the contour of the left portion of the arch in many cases of mitral disease is such that the farthest point to the left of the arch shadow cannot be determined with exactness. In 74 cases in which the shadow could be measured 55 (74 per cent) had a width within 0.5 cm. of the normal average and 9 (12 per cent) were wider by more than 0.5 cm. In 10 cases the measurement was smaller than the normal average by more than 0.5 cm. These figures are practically the same as in the normal group.

Comparison of the normal with groups of pathological cases in which an enlarged basal shadow is known to occur with fair frequency is shown in Table V.

TABLE V

COMPARISON OF NORMAL AND PATHOLOGICAL CASES

MALES AND FEMALES	WITHIN 0.5 CM. OF AVERAGE WIDTH		GREATER THAN AVERAGE WIDTH BY MORE THAN 0.5 CM.	
	CASES	PER CENT	CASES	PER CENT
Normal 178 cases	138	77	23	13
Pathological 138 cases	47	34	81	59
Essential hypertension	16	33	29	60
Hypertension and art. sclerotic aorta	4	21	15	79
Coronary sclerosis, no hypertension	19	53	13	36
Luetic aortitis	1	12.5	7	87.5
Hypertension, all causes	27	29	61	65

In 10 pathological and 17 normal subjects the measurement was smaller than the average by more than 0.5 cm.

There is another significant fact not included in Table V. Of the 23 normal cases which are larger by more than 0.5 cm. only two, or a

little over 1 per cent of the total, have an aortic width greater than the average by more than 1.0 cm. Whereas in the pathological group there are 59 cases, or 43 per cent of the total, showing this degree of increase in width.

No attempt has been made to compare the normal and the pathological shadows in subjects over sixty years old, because it seems impossible to decide what degree of arteriosclerosis is consistent with normal health in people of this age. In 26 men at this time of life without evidence of hypertension the average width of the arch shadow was 6.7 cm. with extremes from 5.0 cm. to 6.9 cm. The average width in 23 men with hypertension was 7.2 cm., the extremes being 5.1 cm. and 9.4 cm.

There are four conditions in which the size of the basal silhouette is increased: syphilitic aortitis, aortic insufficiency, arteriosclerosis of the aorta, and hypertension. The structural change responsible for the increase in the shadow is either dilatation or displacement of the aorta or both of these factors combined. Dilatation of the ascending aorta or arch cannot be estimated in the frontal position. An orthodiagram of the ascending aorta in the right oblique position or of the ascending aorta and arch in the left oblique position will enable one to measure the diameter of the vessel. Fig. 1*B* shows the ascending aorta in the right oblique position in a normal female subject aged twenty-five years. The aortic diameter is 2.3 cm. Fig. 2*B* is an orthodiagram of a dilated ascending aorta in the right oblique position in a patient fifty-five years of age with arteriosclerotic and hypertensive heart disease, the diameter of the vessel being 4.2 cm. Vaquez and Bordet[11] give 2.0 cm. as the normal diameter of the ascending aorta in men at twenty years of age, with a gradual increase to 3.0 cm. in old age. Quain's *Anatomy* gives 2.8 cm. as the diameter of the ascending aorta in adults and states that "the capacity and the thickness of the walls of large arteries increase gradually with advancing years."

Unfortunately the shadow of the aorta in the oblique positions is often too much obscured to be clearly delineated in an orthodiagram. When one has to depend upon the shadow of the frontal plane only, the diagnosis will be based not on the changes in the shadow only, but on the additional evidence obtained from the history and physical examination of the patient.

Arteriosclerosis of the aorta without dilatation of the vessel may cause an increase in the width of the basal shadow in the anteroposterior position because of the fact that the course of the elongated vessel becomes tortuous, compelling the ascending aorta and arch to assume a more sweeping curve similar to that previously described as occurring in stout normal individuals with a high diaphragm. In these cases the left border of the descending aorta is often visualized as a convex curve

below the aortic knob (*Ds* in Fig. 2*A*), and the top of the arch usually reaches a higher position.

Data on rheumatic aortic insufficiency have not been included in Table V because the wide excursion of the aorta so frequently seen in this condition makes it difficult to obtain a drawing of the outline during the diastolic phase and in addition leaves one in doubt whether the aorta is actually dilated or only dilatable under the stress of each systolic discharge from the ventricle. It is also possible that in some instances there may be a wide excursion of the vessel itself without any change in its caliber. A similar excursion of the aorta though not so pronounced is occasionally seen in hypertension and rarely in young neurotic individuals without structural disease of heart or aorta.

Hypertension alone or when associated with some other condition produces increase in the size of the shadow of the width of the arch in 60 per cent to 65 per cent of the cases. When both hypertension and arteriosclerosis are present, the figure mounts to 79 per cent, being exceeded only by luetic aortitis.

CONCLUSIONS

The formula of Hodges and Eyster is the most efficient standard in predicting the transverse diameter of the normal heart.

A heart whose transverse diameter exceeds the predicted diameter by more than 1.0 cm. should be considered enlarged.

In subjects under sixty years of age there is an average width of the aortic arch in accordance with age and sex. This measurement increases with age and is larger in the male than in the female of the same age.

When the average width for the age and sex is exceeded by more than 0.5 cm., the chances are 87 per cent in favor of a pathological cause for the increase in the measurement.

NOTE.—All measurements in this study were obtained by orthodiagraphy with the subject erect.

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A CASE OF TETRALOGY OF FALLOT: CLINICOPATHOLOGICAL OBSERVATIONS; QUANTITATIVE STUDIES OF CIRCULATION RATE AND THE RIGHT-TO-LEFT SHUNT*

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INTRODUCTION

THERE are a number of types of congenital heart disease which cause marked cyanosis; of the cases which live to the age of puberty or early adult life, the so-called tetralogy of Fallot is the most common. This consists of pulmonary stenosis, defect of the interventricular septum, right ventricular hypertrophy and "rechtslage" of the aorta. Our knowledge of the clinical course and pathological anatomy of this lesion-complex has been built up from the analysis of cases that have accumulated in the literature. Further intelligence of this condition must also depend largely upon this method; for, though the tetralogy of Fallot is one of the more common forms of congenital heart lesions, it occurs relatively rarely in the experience of any one individual.

The progress in the study of the physiology of circulation in man that has been made within recent years now makes it possible to analyze the pathological physiology of the circulation in these cases. Such analyses are of considerable significance, both academically and practically. The abnormal conditions present in the tetralogy of Fallot could hardly be reproduced experimentally in animals, and they offer excellent opportunities for studying the adaptation of the body to high grades of oxygen unsaturation. From the practical, clinical point of view, facts about the pathological physiology of these cases may become of value in prognosis. It therefore seems logical to insist that every case of this sort, as of other types of congenital heart disease, should be intensively studied and fully reported, in order to make the case available for the investigator who might undertake to assemble and correlate the accumulated knowledge.

The case which is the subject of this report is that of a young man who died at the age of twenty-three years. He first came to the Montreal General Hospital in November, 1919, at the age of seventeen years, and was subsequently observed in the out-patient department and in the wards of the hospital until the time of his death. The progress of his condition was carefully observed clinically; and during the second and third of his four

*From the Medical Service of Professor C. P. Howard and the Cardiac Clinic, Montreal General Hospital. At the request of Professor Howard and with the kind permission of other members of the staff, who recorded their observations and studies in this case, and of Dr. Maude E. Abbott, who performed the autopsy, the author has collected and correlated all the available data.

periods of stay in the hospital, physiological studies of his circulation were made by Dr. I. M. Rabinovitch.

I. M., male aged seventeen years, born in Russia of Jewish parents; migrated to Canada at the age of five years; came to the hospital's out-patient department and was admitted to the medical service of Dr. H. A. Lafleur on November 18, 1919. He complained chiefly of dyspnea on exertion and dull pain in both axillae. He had been born a blue baby and remained blue, but his physical stature developed normally. He had had dyspnea on exertion ever since childhood. He could never play actively with other children. He received private tuition from the age of seven years and began to attend school at the age of twelve, but made very slow progress in his studies: he could not learn to read or write. At school he was allowed to walk to and from classrooms and to perform other necessary physical exertion at his own slow pace. Of late he had been getting weaker generally and more dyspneic: he had also begun to experience a constant dull ache in each axilla and had developed a cough which was usually unproductive but sometimes brought up whitish, and occasionally blood-stained sputum. On November 14, 1919, he had to stop going to school because of these symptoms.

Neither he nor the members of his family recall his having suffered from any infections or other disease. His mother is alive and well; his father has emphysema; five sisters died, one of peritonitis, the other four of unknown causes.

Physical Examination.—The patient presented the picture of a markedly cyanotic youth; he had a large nose, thick nostrils and lips, large hands with large clubbed fingers, large feet with markedly clubbed toes. His poor personal hygiene and general behavior suggested that he was a mental deficient. Breathing was somewhat labored, but there was no evidence of orthopnea. Conjunctival vessels were dilated and prominent. The teeth were carious and there was much pyorrhea. The palate was highly arched. The throat was injected; the tonsils were not diseased. Some fine crepitations were heard in each axilla; examination of the lungs was otherwise negative.

Heart.—Maximal apex impulse felt in fifth left interspace 10 cm. from the midsternal line; at the base a pronounced systolic thrill was felt with maximum intensity in second left interspace near the sternum. Relative cardiac dullness extended 6 cm. to right and 10 cm. to left of midsternal line in fifth space; there was no increase in supracardiac dullness. Heart sounds were heard with fair intensity at the apex: a rough systolic murmur was traced from the apex to the second left interspace where it was loudest; it was harsh and masked the first sound. This murmur was heard over the entire front of the chest and also over the back: it was not heard over the carotid arteries. The second sound was loud over the aortic area and faint over the pulmonary area. Cardiac rhythm was normal. Systolic blood pressure 152, diastolic 100 mm. Hg. The liver edge was not felt, but liver dullness extended to 4 cm. below the right costal margin in the mammary line. There was no ascites. Moderate-sized lymph glands were felt in the cervical, axillary and inguinal regions. There was slight edema of the lower extremities. Cranial nerve reflexes were normal. There was sustained ankle and rectus clonus. The ocular fundi showed dilated full veins; no pulsation of these was seen.

Blood Examination.—November 18, 1919. Red cell count 7,350,000; white cell count 14,000; hemoglobin, 104 per cent. Differential count: polymorphonuclears 81 per cent, lymphocytes 18 per cent, eosinophiles 0.3 per cent.

X-ray pictures of hands showed increase in soft tissues around terminal phalanges, but no bony changes.

Electrocardiogram: Sinus arrhythmia, rate 75, marked right axis deviation.

Urine: Frequent examinations showed constant presence of albumin varying in amount from a slight trace to a strongly positive evidence.

November 21. At midnight patient had a convulsion; complained of severe headache before and after the convulsion.

November 22. Severe headache continued: 200 c.c. blood drawn from median basilic vein gave him some relief. There was incontinence of urine and feces, apparently due to mental deficiency. Blood pressure 152 systolic, 100 diastolic. (Foul odor to breath.)

November 23. Severe headache continued; patient very restless; occasional vomiting; incontinence of urine and feces; had a convulsion at 5:30 P.M. Lumbar puncture: clear fluid drained under great pressure caused no relief of headache. Examination of spinal fluid: Noguchi, Nonne and Pandy tests all positive.

November 24. As on previous day. Twitching of eyes and face noted. Systolic blood pressure 148.

November 25. Very noisy; attempted to get out of bed; headache seemed less severe.

November 28. He was quiet; headache was milder; red cell count 6,680,000; white cell count 10,000; hemoglobin 106 per cent. Blood pressure 136 systolic, and 106 diastolic.

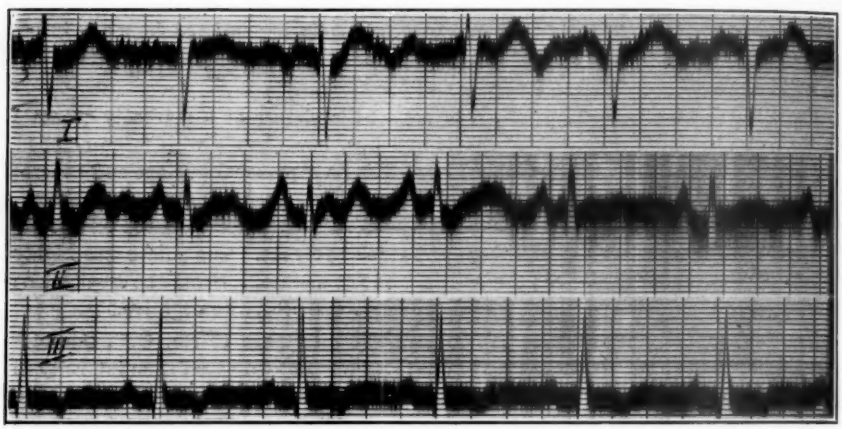

Fig. 1.—Electrocardiogram taken March 7, 1923. Normal rhythm; rate 75; P-R interval 0.21 sec.; P_2 equals 0.5 millivolt and 0.12 second; marked right axis deviation; respiratory variations in height of P-wave.

November 30. No headache; urine incontinence only once; systolic blood pressure 120.

December 7. Headache and vomiting had ceased; felt well; discharged from hospital.

Diagnosis.—Congenital malformation of the heart.

He visited the outpatient department several times in the next three years, and on March 17, 1923, he was readmitted to the hospital under the care of Dr. F. G. Finley. His main complaint was that of diffuse abdominal pain about which no satisfactory history could be elicited. Physical examination revealed some enlargement of liver and spleen; the physical signs of the cardiovascular system were similar to those of 1919; extrasystoles were observed; the blood pressure was 104 systolic and 74 diastolic; there was no edema of extremities. The red cell count was 7,400,000 and the white count 6,500. He remained in the hospital for three weeks during which the abdominal symptoms disappeared.

On November 26, 1924, he entered the hospital under the care of Dr. C. P. Howard. A new symptom was the occurrence of spells of dizziness without loss of consciousness, and no signs suggestive of epilepsy: each attack lasted five or ten minutes, and the

attacks occurred almost daily. These symptoms first appeared in June, 1923. In October of that year he had a bad cold for three weeks during which he coughed up blood-stained sputum.

On November 29, Dr. Howard made the following notes: "The patient presents a most marked grade of cyanosis; it is generalized but, of course, chiefly in the ears, lips, nose, fingers and toes. There is also injection of the conjunctival vessels. The drumstick (clubbed) fingers and toes are very pronounced, the enlargement being largely venous. The nail beds are of a sky blue shade and more intensely blue than the skin of the fingers; the nails are curved and show atrophic changes with dark pigmented areas near the free margins. There is some enlargement of tibiae and fibulae and also to a lesser degree of the radii and ulnae. The bases of the lungs seem quite clear on percussion and auscultation. The thorax shows no precordial bulging;

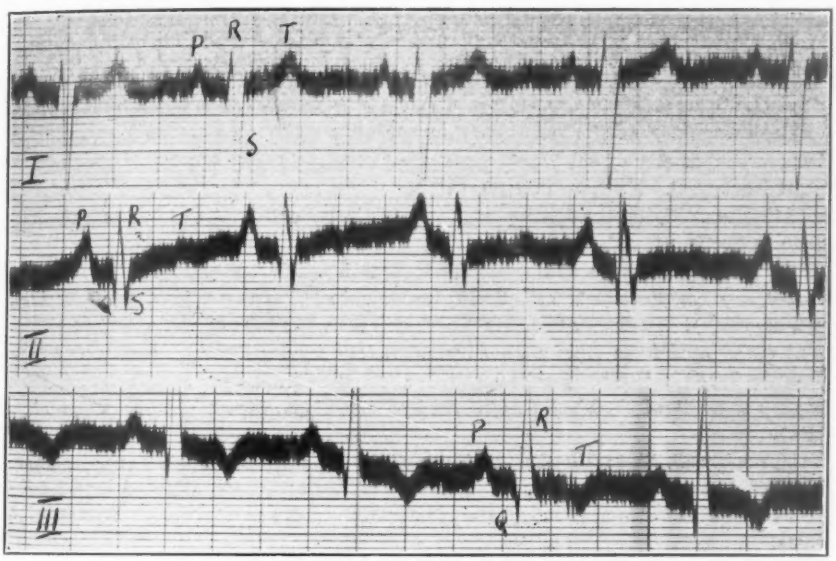

Fig. 2.—Electrocardiogram recorded December 1, 1924; normal rhythm; rate 75; P-R interval 0.2 second; P_2 0.4 millivolt and 0.10 second in duration; marked right axis deviation; premature beats observed but not recorded.

if any asymmetry exists it is due to precordial retraction: the sternum and costal cartilages project prominently. There is no special pulsation visible at apex or base. The maximal apex impulse is palpable in the fourth left intercostal space 8.5 cm. from the midsternum. At the mitral area the systolic shock is felt but there is no thrill. There is a suspicion of a thrill in the second and third left interspaces near the sternum. Over the great vessels there is a well felt diastolic shock. Relative cardiac dullness: upper border over second left interspace; 5.3 cm. to the right and 10.5 cm. to the left of the midsternal line in the fifth interspace. X-ray plate shows enlargement of heart shadow to the right. Heart action is regular and slow. At apex a faint systolic murmur and a very faint diastolic murmur are heard; over the tricuspid area both these murmurs are louder; they are, however, best heard in the second and third left intercostal spaces near the sternum. The second sound is loud and of equal intensity over the pulmonic and aortic areas. The radial pulses are synchronous and equal. The liver just reaches the right subcostal margin; it is not enlarged and not tender. The spleen is moderately enlarged, firm, but not tender."

On December 11 he had an attack of loss of consciousness which was described as follows by Dr. E. S. Mills: "After supper, while the patient was sitting in a chair, he suddenly felt dizzy, then fell to the floor with convulsive movements of the arms and legs, frothing at the mouth, coughing and expectorating small quantities of bright red blood. He was put to bed by attendants. When seen, about a minute after the onset, he was found lying in bed, unconscious; respirations were deep and rapid, blood-tinged froth oozed from the mouth. The pupils were dilated and fixed. The knee jerks were absent and the arms and legs in a state of flaccid paralysis. In about five or six minutes he began to make efforts to get out of bed, and resisted as the blood pressure was being taken. This was found to be 148 systolic and 110 diastolic. Consciousness slowly returned, the knee jerks became active, and the pupils assumed their natural size. During this attack the cyanosis was most intense. He had never had such an attack before."

During this period of stay in the hospital a number of laboratory procedures done on previous occasions were repeated.

The electrocardiogram (Fig. 2) showed normal rhythm, rate 75, marked right axis deviation; high P-wave in Lead II, and slurring and notching of the R-wave in Lead II. Some extrasystoles, most probably auricular, were observed but not recorded.

X-ray examination of the heart (November 28, 1924) revealed an increase in the transverse diameter of the heart, especially to the right, and the left auricle also appeared enlarged. X-ray examination of the hands showed, as before, fullness of the soft tissues overlying the distal phalanges. There were no bone changes and the knees were perfectly normal.

Wassermann reaction of the blood was negative. November 29, 1924: Red blood cells 9,200,000; white blood cells 8,600; hemoglobin 146 per cent (calculated from oxygen capacity). December 2, 1924: Red blood cells 10,280,000; hemoglobin 205.5 per cent (calculated from oxygen capacity determined by Dr. Mills). Hematocrit 0.775. January 7, 1925: Red blood cells 9,090,000; hemoglobin 187.2 per cent (calculated from oxygen capacity of the blood determined by Dr. Mills on the basis 18.5 c.c. O_2 = 14 gm. Hb.).

November 28, 1924: Blood urea nitrogen 17.0 mg.; and sugar 0.125 mg. per 100 c.c. blood. Frequent examinations of urine showed the specific gravity to vary between 1.018 and 1.021, few pus cells and phosphates in the sediment, but no albumin, sugar or casts.

December 1, 1924: Dr. I. M. Rabinowitch made observations required for calculating the circulation rate; these are described below.

January 27, 1925: Dr. E. S. Mills made the following notes: "The patient has been up and about in the ward for the past three weeks. He has suffered from frontal headaches from time to time, but on the whole has enjoyed fairly good comfort. His appetite is good, bowels are regular. He now has no dyspnea at rest. There has been no apparent change in the degree of cyanosis. Physical examination: lungs clear; heart—apex impulse in fifth left intercostal space 8 cm. to left of midsternal line. Relative cardiac dullness begins at third left rib, and in fifth space extends 9 cm. to the left and 5.5 cm. to the right of the midsternal line; there is a faint thrill in the second and third left intercostal spaces; the heart sounds are as on admission. There is no edema of the extremities. The patient is discharged from the hospital to go to his home."

November 25, 1925: The patient was readmitted to Dr. Howard's service. He complained of marked dyspnea on exertion; he could not walk one hundred yards without having to "stop for breath" and he has been using three pillows to sleep on, to avoid the dyspnea he has on lying flat. The seizures of dizziness and unconsciousness have increased very much in frequency; he was free from them for the first four months after leaving the hospital in January, 1925, they then began to come on again and

finally occurred once or twice daily. They occur only during the daytime, usually when he is standing; he has never had one at night while lying in bed. The occurrence of a seizure bears no definite relation to any of his habits or activities. He has lately suffered severely from supraorbital headaches; there has been some coughing, but without expectoration. His hands and feet are always cold, but he has not experienced any numbness. For many months he has not stirred out of the house for fear of having a fit while on the street. Physical examination revealed signs similar to those of November, 1924.

November 30, 1925: While in bathroom he vomited and felt faint; he was found unconscious, very deeply cyanosed and breathing stertorously; pupils at first were dilated, did not react to light. The abdominal reflexes could not be elicited but the tendon reflexes were all present; there was no spasticity nor any undue degree of flaccidity. There was no biting of the tongue and no frothing at the mouth. Blood pressure 110 systolic and 60 diastolic; pulse 72 per minute and irregular. The attack lasted ten

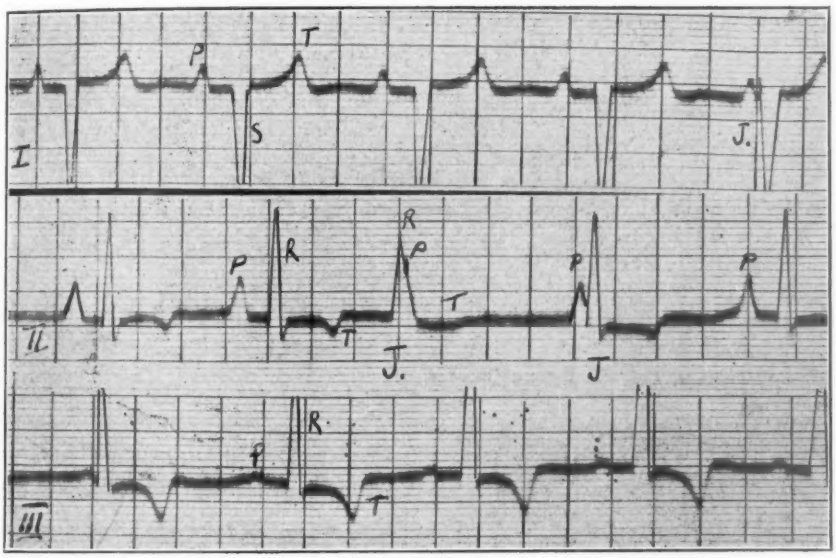

Fig. 3.—Electrocardiogram taken December 1, 1925. Normal rhythm interrupted by premature beats originating at different points in junctional tissue marked "J," in Leads I and II; rate 75. The P-R interval 0.2 second; the P-wave in Lead II is 0.5 millivolts and 0.1 second; marked right axis deviation.

minutes, the patient after regaining consciousness was apparently very much weakened for he soon fell asleep. Otological examination on this day revealed bilateral otitis media.

December 4, 1925: The patient seemed more comfortable in the past four days. Occasional extrasystoles were detected. Oxygen administered by funnel method for fifteen minutes did not lessen cyanosis to any appreciable degree.

December 5, 1925: Inhalation of oxygen under pressure for thirty minutes caused no change in cyanotic color.

Blood examination November 25, 1925: Red blood cells 8,100,000; white blood cells 9,300; hemoglobin 120 per cent (Dare).

December 4, 1925: Red blood cells 8,630; white blood cells 6,850. Differential count: polymorphonuclears 76 per cent, large lymphocytes 4 per cent, small lymphocytes 17 per cent, eosinophiles 3 per cent. No abnormalities in shape of red cells.

Hemoglobin 194.7 per cent (van Slyke). Urea concentration factor (Rabinowitch) equals 41. Urea nitrogen 20. Creatinin 1.76. Oxygen capacity of blood 36.02 vols. per cent.

December 8, 1925: The following note was made by the house officer, Dr. Webster: "At 8 P.M. patient was sitting up in bed, apparently feeling better than during the

Fig. 4.—*A*, superior vena cava; *B*, inferior vena cava; *C*, patent foramen ovale; *D*, sinus coronaris (anomalous tendinae replacing thebesian valve); *E*, right ventricle seen through defect; *F*, conus arteriosus.

Fig. 5.

Fig. 6.

Fig. 5.—The conus arteriosus (showing fused semilunar valves, the raphes at *A*, *B*, and *C*).

Fig. 6.—The left ventricle, showing partial fusion and ulceration of the semilunar valves of the aorta, which roof the defect in the interventricular septum.

past few days. Suddenly the nurse noticed blood coming from his mouth. The patient called to her and shortly afterward lapsed into one of his typical fits of unconsciousness. He had incontinence of urine and feces, his teeth were clenched and the pupils dilated. The first hemorrhage consisted of about 8 ounces of frothy red blood. At about 8:15 P.M., while still unconscious, he had a second hemorrhage. About four ounces of frothy (pulmonary) blood issued from the nose because of the clenched teeth firmly closing his mouth. The patient did not regain consciousness, the jaws remained rigid." Thus the patient died.

SUMMARY OF POST-MORTEM REPORT

Autopsy was performed and findings were described in full detail by Dr. Maude E. Abbott.

Summary:

1. General congestion and cyanosis of all tissues.
2. Marked clubbing of all fingers and toes with incurving nails.
3. Foramen of Winslow obliterated.
4. Lesser peritoneal cavity closed by adhesions.
5. Enlarged liver, congested and firm.
6. Hypertrophied kidneys, with cortex-medulla ratio increased.
7. Markedly hypertrophied and congested spleen.
8. Great distention of stomach with black tarry material.
9. Marked hypostatic congestion.
10. Evidence of pulmonary hemorrhage in both lungs, with blood-filled bronchi.
11. Heart: This case presents a classic example of the so-called tetralogy of Fallot, in which a pulmonary stenosis and hypoplasia of the developmental type is associated with a defect of the interventricular septum just anterior to the undefended space, and with dextra-position of the aorta which rides above the defect, receiving the blood from both ventricles; and this combination is the commonest condition in cases of congenital cyanosis with clubbing reaching adult life. The chief points of additional interest are, the compensatory changes in the infundibular cusps of the tricuspid valve, the sclerosing process on the conus wall and pulmonary and tricuspid valves, and the inflammatory fusion of aortic cusps with recent endocarditis; also the dilatation of the ascending aorta with hypoplasia of the trunk below in the absence of coaretation.

DETERMINATION OF THE VENOUS ARTERIAL SHUNT

The observations presented in Table I and the calculations described in Table II were made by Dr. I. M. Rabinowitch.

Calculation of the Venous Arterial Shunt

Let X = shunt, expressed in per cent of total cardiac output.
a = reduced hemoglobin content of arterial blood.
V = reduced hemoglobin content of venous blood.
T = total hemoglobin (100 per cent).
p = reduced hemoglobin in pulmonary vein blood.

Then

$$a = (1 - X)\ p\ T + X\ V.$$

For the value of V either v_1, the reduced hemoglobin content of arm vein blood, or v_2, that estimated for mixed venous blood, may be used.

DISCUSSION

The Venous Arterial Shunt.—The clinical and anatomical features of the tetralogy of Fallot obviously indicate that during life the arterial

TABLE I

		MAR. 16, 1923		DEC. 1, 1924
		BASAL	AFTER EXERCISE	BASAL
A	Oxygen content of arterial blood	7.32 vols. %	5.16 vols. %	16.9 vols. %
A_1	Oxygen capacity of arterial blood	21.96 vols. %	21.96 vols. %	26.3 vols. %
a	Reduced hemoglobin in arterial blood	66 %	76.5 %	35.8 %
V_1	Oxygen content of arm vein blood	3.82 vols. %	0.66 vols. %	9.8 vols. %
v_1	Reduced hemoglobin in arm vein blood	83 %	97 %	62.8 %
V_2	Oxygen content of mixed venous blood (A-5)*	2.32 vols. %	0.16 vols. %	11.9 vols. %
v_2	Reduced hemoglobin of mixed venous blood	89.95 %	99.27 %	55 %
P	Oxygen content in pulmonary vein blood (.955A_1)†	20.97 vols. %	20.97 vols. %	25.1 vols. %
p	Reduced hemoglobin in pulmonary vein blood	0.045 %	0.045 %	0.045 %
	Oxygen consumption per minute	241.0 c.c.	328.0 c.c.	281.0 c.c.
	Metabolic rate	+7 %		+22 %

*5 vols. % is assumed to be the amount of oxygen utilization in the tissues according to Lundsgaard.

†It is assumed that the process of oxygenation in the lungs is normal.

TABLE II

EQUATION OF VENOUS ARTERIAL SHUNT

	MAR. 16, 1923		DEC. 1, 1924
	BASAL	AFTER EXERCISE	BASAL
$a = (1 - X)\ p\ T + X\ v_1$	78.3%	77.85%	53.7%
$a = (1 - X)\ p\ T + X\ v_2$	72%	75.8%	62.0%

stream consists of a mixture rich in reduced hemoglobin. The exact proportions of reduced and oxygenated hemoglobin in this mixture must vary in different individuals under similar conditions of body activity, depend-

ing upon the relative size of the pulmonary and aortic orifices, the size of the septal defect and the position of the aortic orifice in relation to its communications with the right and left ventricular cavities. Other factors, such as the efficiency of ventricular musculature, the influence of associated anomalies, as, for example, collateral pulmonary circulation through bronchial arteries, patent ductus arteriosus, patent foramen ovale, hypoplasia of the aorta, etc., must also play important rôles in determining the nature of the mixed blood in the arterial stream. One may therefore expect to find differences in the estimates of the arteriovenous shunt made in different cases. We have been able to discover reports of such studies in but six cases.

The first report of circulation rate studies and estimation of the venous arterial shunt in a case of tetralogy of Fallot is that of Weiss and Löwbeer[2] (1924). Abbott[3] quotes a case investigated at the Massachusetts General Hospital by Bock, Field and Stoddard in 1924. The observations in our case were made by Dr. I. M. Rabinowitch in 1923 and 1924; our case is the only one in which an attempt was made to observe the effects of exercise on the circulation rate and on the shunt. Dautrebande, Marshall and Meakins[1] (1929) report studies on three cases in one of which observations were made in 1922. Richards, Riley and Hiscock,[4] in the most recent report, include studies of the effect of keeping the patient in an oxygen chamber, but do not calculate the shunt. Abbott quotes the data and methods of calculation described by Weiss and Löwbeer and by Bock and his associates. Dautrebande, Marshall and Meakins calculated the venous shunt by the two methods of Bock and his associates in two of their cases and by all three methods in the third case; the results varied so widely that they concluded "it was found impossible to obtain reliable determinations of the venous, or right to left, shunt." We have applied additional methods of calculating the shunt to the data of Weiss and Löwbeer's case and of our case and have tabulated the results obtained by various methods in the six cases (Table IV). In only one of the cases in the series of Dautrebande, Marshall and Meakins were data available for the application of the Weiss and Löwbeer method. In all cases the data permit calculation of the shunt by the following equation.

$$A = \frac{V}{100} + \frac{P(100 - X)}{100}$$

in which $A = O_2$ content of arterial blood
$V = O_2$ content of venous blood
$P = O_2$ content of pulmonary vein blood.

In each case (A) the O_2 content of radial artery blood was determined directly. For the O_2 content of venous blood either of two values is available, namely, (V_1) the oxygen content of arm vein blood determined by experiment, or (V_2) the assumed mixed venous blood value calculated by

subtracting 5 vols. per cent from the arterial O_2 content (Lundsgaard and van Slyke,[5] average oxygen utilization by the tissues is 5 per cent). For estimating the O_2 content of pulmonary vein blood it is also possible to choose between two values; it may be assumed that oxygenation proceeds normally so that the blood entering the pulmonary veins is 95.5 per cent saturated (P_1) or the observations of Campbell, Hunt and Poulton[6] may be taken into consideration and the blood may be assumed to be 85 per cent saturated (P_2). Thus, using the above formula, four different calculations of the shunt may be made in each case, thus—

1. $A = 0.01\ (V_1)X + (100-X)\ (0.01)P_1$
2. $A = 0.01\ (V_2)X + (100-X)\ (0.01)P_1$
3. $A = 0.01\ (V_1)X + (100-X)\ (0.01)P_2$
4. $A = 0.01\ (V_2)X + (100-X)\ (0.01)P_2$

TABLE III

VENOUS ARTERIAL SHUNT CALCULATED BY FOUR DIFFERENT EQUATIONS

	MARCH 16, 1923		DEC. 1, 1924
EQUATION	BASAL	AFTER EXERCISE	BASAL
1	79.5%	77.8%	53.4%
2	73.0%	76.0%	62.0%
3	76.4%	75.0%	43.4%
4	69.3%	73.0%	52.2%
Maximum % variation	14.5%	8%	42.8%
Minimum % variation	2%	1.3%	2.2%

The differences in the estimated shunt depending upon the nature of the assumptions made in the calculation, the four equations were applied to the data of our case (Table III). Equations 1 and 2 are those used by Bock, Field and Stoddard[3] in two separate experiments. In all of the cases the data allowed calculation of the shunt by equation 2 (Table IV), with the exception of the Weiss and Löwbeer[2] case and one of the two experiments in the case of Bock and his associates equation 1 could also be applied.

The equation used by Rabinowitch for the calculation of the shunt in our case is the same as that of Bock, Field and Stoddard, only Rabinowitch applies the values for reduced hemoglobin instead of those for oxygenated hemoglobin. Hence calculations by the method of Rabinowitch lead to results essentially the same as those of equations 1 and 2.

A comparison of the results obtained in each case by different methods of calculation (Table IV) reveals variations that range between 2 and 215 per cent. If the results are viewed in the light of these two extremes, Dautrebande, Marshall and Meakins may be considered as justified in concluding that no reliable calculation of the shunt could be made. The

instance of 215 per cent variation occurs in one of their cases. All the other cases also show such wide variations that one must question whether these estimates of the shunt have any significant value. On the other hand, the estimates made with equation 2* present figures which seem to represent the magnitude of the venous arterial shunt quite reasonably when due allowance is made for anatomical differences in the different cases. Furthermore, at present, equation 2 seems to offer the most reliable formula for calculating the shunt, since the possible errors in the data required are smaller than in either of the other two formulae. Thus in equation 1, the oxygen content of arm vein blood is used to represent that of mixed venous blood in the right auricle. Now it has been shown by a number of observers that the oxygen content of arm vein blood is likely to vary widely and that it is not truly representative of mixed venous blood. A crucial factor of the Weiss and Löwbeer[2] method is the estimation of the pulmonary blood flow by the nitrous oxide method; the experimental error of this procedure is so great as to make it unsuitable for the quantitative estimation of total circulation and of the shunt in a given case, although it may be of value for studies of a comparative nature. The sources of error for all methods seem to be in the limitations of the technic of measuring cardiac output in man rather than in the validity of the equations. Table III illustrates the wide variations in the figures of the estimated shunt when different assumptions are made as regards oxygen content of mixed venous blood and of pulmonary vein blood. The greater uniformity of the figures obtained with equation 2 is due to the fact that the two most important factors in the data required were obained by a technic that may be said to have a low experimental error even when used by different individuals; the quantitative estimation of the oxygen content of the mixed venous blood is obtained by assuming the oxygen utilization to be 5 vols. per cent.

The clinical and pathological features of the tetralogy of Fallot offer evidence from which one may deduce an approximate estimate of the proportions of "venous" and "arterial" blood which make up the mixture that enters the aorta from the heart. The large right chambers and the relatively small left chambers of the heart indicate that the ouput of the right heart is much greater than that of the left. Second, the position of the aortic orifice and its patent communication with the right ventricle, and on the other hand, the smallness of the pulmonic orifice and the high resistance at this aperture, point to a generous flow of "venous" blood into the aorta. Basing an estimate of the amount of venous blood that enters the aora on these considerations it may be judged to be 50 per cent or more of the total cardiac output. It, therefore, seems to be a significant fact that the values obtained by the application of equation 2 to the data in

*Dr. Maude E. Abbott has drawn my attention to the fact that in 1924 Dawson[12] suggested the method of calculation represented by this equation on purely theoretical grounds.

the different cases range between 45.4 per cent and 76 per cent. It now appears reasonable to consider the magnitude of the venous arterial shunt, under basal conditions, to be at least 40 per cent of the total cardiac output into the aorta.

Clinical observers have invariably described an increase in cyanosis on exertion in cases of tetralogy of Fallot. With increase in cardiac output per minute during exercise it is most likely that the free communication between the right ventricle and the aorta and the very restricted communications with the pulmonary circulation make for an increase in the proportion of venous blood in the arterial stream. Another likely factor in the production of this increase in cyanosis is the acceleration of oxygen utilization in the tissues as a compensatory mechanism. Thus the proportion of reduced hemoglobin in capillary blood must become considerably increased. The single determination of the effect of exercise in our case reveals a relatively small increase in the shunt by equation 2, and a very small diminution by equation 1; the former figure seems to be the closer approach to the truth, although the increase is smaller than one might expect to find.

During the last six months of the life of our patient there was striking progressive increase in cardiac failure: orthopnea appeared, he suffered from attacks of pulmonary congestion similar to those met with in cases of mitral stenosis, and he died in the course of one of these attacks. The last experiment for the estimation of circulation rate and venous arterial shunt was performed about a year before his death; therefore in comparing the results of this experiment with those of the first data obtained twenty months previously, it becomes necessary to consider the factor of diminished myocardial strength, especially of the right ventricle. The venous arterial shunt estimated in December, 1924, is at least 15 per cent smaller than that determined in March, 1923. This diminution may be attributed to a disproportion in the myocardial failure of the two ventricles. As the right ventricle loses strength in greater degree than the left, the venous arterial shunt also diminishes. However, the total cardiac output also becomes decreased and pulmonary circulation becomes less efficient so that in spite of the relatively smaller shunt the circulatory mechanism is weakened.

Circulation Rate.—The amount of blood put out by the heart into the aorta per minute may be estimated by applying the following equation:

$$C = \frac{M}{U} \times 100$$

wherein C = circulation rate, M = oxygen consumption per minute expressed in cubic centimeters, and U = the oxygen utilized by the tissues expressed in volumes per cent. The value for U may be taken as 5 (U_2) according to Lundsgaard and van Slyke[5] or it may be calculated as the dif-

ference (U_1) in oxygen content between the arterial and arm vein bloods determined by experiment. Using U_2, the circulation rates in cubic centimeters per minute, determined in our case are 4,820 at rest, 6,560 after exercise in March, 1923, and 5,620 at rest in December, 1924. Using U_1, the corresponding rates are 6,887, 7,288 and 4,014 respectively. The increase following exercise is within expected limits. The rates for basal conditions estimated from the experiments in 1923 and 1924 are so discordant that they cannot be compared logically. It is more likely that as the result of right ventricular myocardial failure, evidenced by the clinical observations and by the diminution in the venous arterial shunt, the total circulation rate was smaller in December, 1924, than twenty months previously when cardiac function was more efficient. Weiss and Löwbeer[2] estimated the circulation rate as 7,080 c.c. per minute in their case, under basal conditions; this is a somewhat higher figure than any of ours.

TABLE IV

VENOUS ARTERIAL SHUNT CALCULATED BY DIFFERENT METHODS, EXPRESSED IN PER CENT OF TOTAL CARDIAC OUTPUT

CASE	EQUATION NO. 1	EQUATION NO. 2	WEISS AND LÖWBEER	VARIATION	
				MAXIMUM	MINIMUM
Dautrebande et al.[1]	40.5	68.8		70	41.0
Dautrebande et al.[1]	34.0	58.0		70	41.0
Dautrebande et al.[1]	19.8	45.4	62.4	215	27.2
Weiss and Löwbeer[2]		56.2	69.0	23	10.8
Boek et al.[4] Jan. 15, 1924		70.7			
Boek et al.[4] Jan. 21, 1924	69.2	48.83		41.7	29.0
Our case Mar. 1923, Basal	79.5	73.0		8.8	8.3
Our case Mar. 1923, Post exercise	77.8	76		2.37	2.31
Our case Dec. 1924	53	62		17.0	14.5

Growth and Development.—The mother of our patient has told us that he was blue from birth onwards, but that he grew in stature quite normally and, moreover, that he was physically strong. Mentally, however, he was very different from the other children in the family. He was given private tuition at home and also attended school, but was unable to learn the most elementary things and grew up illiterate, although he was intelligent enough to understand and carry out simple commands as well as to attend to his personal needs. He made himself useful in helping his father attend to the chores of a small grocery shop, but was unable to assist in waiting upon customers. The question as to whether the mental deficiency might be attributed to the cause of the marked cyanosis is suggested by the fact that Haldane[7] describes psychic effects including mental dullness during relatively high grades of anoxemia. The adaptation of the tissues to low

oxygen saturation of the blood in our case will be discussed below; it will then become apparent that the degree of cyanosis is not a true measure of anoxemia and that the tissues were provided with sufficient oxygen to maintain normal body metabolism within certain limits of activity. Dr. Maude E. Abbott, from her intimate knowledge of the literature, as well as from personal experience of similar cases, has gained the impression that patients with congenital cyanosis are usually of normal and, not infrequently, of supernormal intelligence. The subject of Boek, Field and Stoddard's observations, whom one of us (H. N. S.) observed during life, was a man of thirty-two years, with cyanosis and heart similar to that of our case; he was unusually bright as a business man and very witty. There seems to be no direct relationship between the cyanosis and mental deficiency in our case.

Adaptation of the Body to the Cardiac Anomaly.—The intense grade of cyanosis from birth suggests a very grave degree of oxygen want, so that one would expect stunted growth in body and mind in these cases. The fact that they are usually normal in this respect indicates the high degree of adaptation to the pathological condition that causes the cyanosis. Another remarkable feature of these cases is that many survive to the age of puberty and not a few go beyond the second and third decades. An analysis of all the factors concerned in the adaptation of the functions of the body to abnormal conditions of circulation must necessarily be limited at the present time for want of knowledge.

In the heart itself, the congenital pulmonic stenosis is accompanied by a compensatory hypertrophy of the right ventricle. In our case, this was diagnosed clinically on ample grounds, namely, enlargement of the heart to the right as determined by percussion and x-ray examination, and in addition, marked right axis deviation shown in the electrocardiogram. The post-mortem examination showed a very thickened and enlarged right ventricle, and a less thick and smaller left ventricle. This cardiac hypertrophy, particularly of the right ventricle, is the chief mechanical factor of adaptation; in virtue of it the lungs received relatively sufficient blood in spite of the small pulmonary valve orifice. A conservative estimate of the circulation rate, under basal conditions, was determined as 4820 c.c. per minute on one occasion, and 5620 c.c. on another, whereas after exercise it was found to be 6560 c.c. per minute. These figures closely resemble those obtained in the normal and thus indicate that the cardiac hypertrophy was quite effective in compensating for the mechanical disabilities.

The next obvious factor of adaptation is the marked degree of erythrocytosis; in our case there was an increase of 50 to 100 per cent in red cells without a corresponding increase in white cells, and a hemoglobin content always more than 100 per cent. On one occasion the hemoglobin content was calculated from the oxygen capacity of the blood and found to be 194.7 per cent, with a red cell count of 8,630,000; and on another occasion

205.5 per cent, with a red cell count of 10,280,000. From studies of the adaptation of normal individuals to living in high altitudes, it has long been known that an increase in red cells and hemoglobin takes place in order to compensate for the lower partial pressure of oxygen in the atmosphere. An individual who is not adapted to high altitudes presents symptoms of anoxemia when exposed to a lowered partial pressure of oxygen, that is to say, symptoms of want of oxygen in the body tissues. In a case of tetralogy of Fallot, the right-to-left shunt results in an admixture of "venous" and "arterial" blood which reduces the oxygen content of the mixed blood considerably below that of "arterial." Thus the blood of the systemic arterial stream is characterized by a sufficiently low oxygen content to cause marked cyanosis. But the basal metabolic rate measured on two occasions in our case was +7 and +22 per cent; in other words, the body tissues were being supplied with ample oxygen and were not suffering from anoxemia. It appears, therefore, that the degree of cyanosis is no index to the degree of anoxemia in a case such as ours. The increase in the number of red cells and the amount of hemoglobin raises the oxygen capacity of the blood so that it becomes possible to maintain an oxygen tension in the capillaries sufficiently high to provide the tissues with their normal oxygen requirement within certain limits of body activity.

The duration of life in 73 cases of tetralogy of Fallot analyzed by Abbott[8] varied from eleven days to thirty-six years. White and Sprague have reported the case of a noted musician who lived to his sixtieth year. From the above discussion of the main factors of adaptation it would appear that the duration of life is determined by the amount of right-to-left shunt on the one hand, and the erythrocytosis on the other. The amount of the right-to-left shunt is determined by the mechanical features in the heart, namely, the size of the pulmonary valve orifice, the size of the interventricular septal defect, and the relation between the pressures developed in the right and left ventricles. Under given intracardiac conditions the efficiency of the myocardium plays the central rôle in determining the duration of life, since upon it depend the maintenance of a requisite circulation rate and the restriction of the right-to-left shunt to within physiological limits. There are, no doubt, other changes in the blood and in the tissues which also make for maintaining normal metabolism.

Limits of Function of the Circulatory System.—From early childhood the patient was in the habit of walking at a slow pace; if he walked rapidly, he had the discomfort of breathlessness. After short but rather great exertion, like lifting a heavy box, he had to stop to recover from dyspnea in the form of rapid shallow respirations. During his stay in the hospital ward, it was noticed that the cyanosis became more intense when he changed from the upright to the recumbent posture, when he performed moderate exercise sufficient to induce dyspnea and also during the attacks described by Dr. Mills and Dr. Webster. The intensification of the cyano-

sis on change of posture may be attributed to venous congestion in the head, resulting from the effect of gravity. This, associated with exertion, indicates that the patient had, in some degree, a reserve mechanism present in normal people, namely, the ability to develop an oxygen debt, but this mechanism in our case could function only within much narrower limits than in the normal individual. The experiment performed on March 16, 1923, gives some clue to the limitations of the patient's power to provide his tissues with oxygen during exertion. Before exercise (walking up and down the ward) the arterial O_2 content was 7.32 vols. per cent and after exercise it was 5.16 vols. per cent. The O_2 content of venous blood before exercise was 3.82 vols. per cent; after, 0.66 vols. per cent. The response to exercise in this experiment exemplifies the very narrow limits of reserve within which the activities of the patient had to be maintained in order that he might be comfortable. The considerable oxygen debt of (328-241) 87 c.c. per minute was accumulated by the ordinary exertion of walking for a few minutes. The increased circulation rate associated with exercise is greatly restricted in its effectiveness by the existence of the venous arterial shunt. Moreover, it is very likely that with increase in cardiac output, the magnitude of the shunt becomes augmented both relatively and absolutely. If, to these disabilities, that of myocardial failure is added, the main compensatory mechanism lies with peripheral circulation: the margin of oxygen desaturation of the blood by the tissues is widened so that the oxygen debt rapidly accumulates in the presence of a very deficient pulmonary circulation. On one occasion oxygen was administered to the patient by the funnel method when he was at rest in bed; no effect on the cyanosis or on respiration could be detected. Richards, Riley and Hiscock[4] observed their patient during the three days that he remained in a Barach oxygen chamber and could not find any evidence of a significant beneficial effect. "The arterial oxygen saturation rose only 5 per cent, scarcely more than the change that would occur in a normal person."

Miscellaneous Symptoms and Signs.—On his first visit to the hospital, the patient complained among other things of abdominal distress unrelated to food or exertion. Post mortem, the lesser peritoneal cavity and the Foramen of Winslow were found to be obliterated by adhesions. Whatever may have been the etiology of the inflammatory process which the adhesions represented, these findings probably explain the abdominal distress.

During the whole period of observation the urine was frequently examined and always found to contain albumin, sometimes in smaller at other times in larger quantities. Casts, red blood cells and pus cells, though always present, were never abundant. The specific gravity varied from 1.014 to 1.021. On November 28, 1924, blood urea nitrogen was 17 mg. per 100 c.c. On November 25, 1925, blood urea nitrogen was 20 mg. per 100 c.c., creatinin 1.76 mg. per cent, and the urea concentration factor

(Rabinowitch) 41. These observations on the blood are those of normal kidney function, but persistence of albuminuria with some red cells and casts are suggestive of some functional abnormality in the kidneys. Furthermore, the hypertension, observed almost invariably, would seem to point to some form of nephritis. At autopsy the kidneys showed evidence of venous congestion and parenchymatous degeneration; coupled with the normal blood findings this must exclude the possibility of nephritis. It is highly probable that the hypertension may have been due to the relatively high degree of aortic hypoplasia alone, or to some unknown factor associated with the erythrocythemia, similar to that which occurs in some cases of polycythemia rubra vera. Venous congestion in the kidneys, associated with erythrocytosis, as well as the abnormally low oxygen tension of the blood with its effect on tissue metabolism, explain the parenchymatous degeneration with persistence of albuminuria, red cells and casts.

All the observers of our case were impressed by the very pronounced degree of clubbing of the fingers and toes. Repeated x-ray examinations showed no evidence of changes in the bones of the fingers and toes, although such changes have been described. During the whole period of six years the patient was seen by different observers at different times and so no accurate statement as to whether the clubbing increased during that time can be made.

The Heart Sounds and Murmurs.—The notes made by various observers at different times revealed considerable lack of uniformity in the description of the cardiac sounds and murmurs. The unusual nature of the case and the clinical interest that the condition of the heart must have aroused in the observers make it reasonable to assume that the auscultatory signs were studied and recorded with particular care. This would tend to diminish the significance of the personal equation in comparing the records of these observations, but it must be included as one of the factors responsible for the differences found.

A systolic murmur was heard by all observers and was likewise invariably found to be loudest over the pulmonic area. The loudness of this murmur and the areas over which it was heard were variously described. In 1919 and 1923 it was described as harsh, loud, and audible all over the front and back of the chest. In 1924 a systolic murmur at the apex was recorded as faint; and, for the first time, a faint apical diastolic murmur was also mentioned: both these murmurs "are louder over the tricuspid area; they are, however, best heard in the second and third left intercostal spaces near the sternum." In 1919 the second sound was described as "loud over the aortic area and faint over the pulmonic area"; in 1924 "the second sound is loud and of equal intensity over the pulmonic and aortic areas." A systolic thrill over the pulmonic area was felt by all observers except one. In 1925 the only diastolic murmur is a "questionable presystolic murmur."

The post-mortem examination of the heart revealed at least three possible causes for a systolic murmur and two for a diastolic murmur. The congenital stenosis of the pulmonary artery, the interventricular septal defect, and the rheumatic aortic stenosis, each might be responsible for a systolic murmur. The fact that the observed murmur was loudest in the second left interspace near the sternum makes it most probable that it was due almost entirely if not entirely to the pulmonic stenosis. It appears to have been very much louder in 1919 and 1923 than in 1924 and 1925; this change may be attributed to right ventricular myocardial failure, but not without certain reservations. The systolic blood pressure was as high in 1924 when the apical systolic murmur was described as "faint," as it had been in previous years when the murmur was so loud that it was heard all over the chest. In this case the right ventricle played as great a rôle as the left ventricle, and perhaps a greater one, in maintaining systemic blood pressure; so that the blood pressure measured in the arm is indicative of the pressure in the right ventricle and of the force with which blood was projected through the stenosed pulmonary orifice. Since this force was not less in 1924 than in 1919, one may doubt whether right ventricular failure per se was responsible for the diminished loudness of the murmur. Another factor in determining the variations in loudness of the systolic murmur which deserves being mentioned is increase in peripheral resistance in the pulmonary circulation. Furthermore, if it is assumed that systolic murmurs were also produced at the slightly stenosed aortic valve and at the ventricular septal defect, diminished and increased loudness due to interference of sound waves from the three different sources may be considered as a possible explanation for the variations that were observed in the systolic murmur.

On March 17, 1923, Dr. Finley noted, "No diastolic murmur is heard," while on November 26, 1924, Dr. Howard found a diastolic murmur at the apex which was louder at the tricuspid area, and loudest over the second and third left interspace near the sternum. Between 1919 and 1924, no observer heard a diastolic murmur in spite of the fact that at autopsy a fixed pulmonic orifice was found. This may be explained in the following manner: the thinness of the pulmonary artery indicates that the difference between the pressures in the right ventricle and in the pulmonary artery during ventricular diastolic was not such as to occasion a stream of blood from the artery into the ventricle, sufficiently forceful to produce a diastolic murmur. The appearance of the diastolic murmur in 1924 must be associated with the rheumatic inflammatory deformity of the aortic valve; and this must have developed in the interval between March, 1923, and November, 1924. Judging by the blood pressure recorded a year later, shortly before his death, there could not have been much disturbance of function due to this deformity of the aortic valve.

On one occasion the spinal fluid was examined and found to issue forth at high pressure. The Noguchi, Nonne and Pandy tests for globulin were

all positive. In view of the negative Wassermann, one is led to suspect that this increase in globulin content of the spinal fluid may have been due to causes similar to those which produced the urinary findings described above. This possibility is very likely, particularly since the secretion of both fluids is dependent upon the permeability of membranes, which may have been rendered more permeable to proteins by the low oxygen saturation of the blood.

Encephalopathic Phenomena.—The pathological physiology of the cerebral symptoms cannot be discussed in the light of autopsy findings because, unfortunately, the brain was not examined. Similar cerebral phenomena have been described in cases in which the brain was examined without finding any anatomical changes to account for them. Attempts have been made to explain the mechanism of symptoms such as these on other grounds. Vaquez[10] mentions the possibility that they may be attacks of Stokes-Adams syndrome. The clinical picture of unconsciousness with convulsive movements of the limbs in our case does bear some resemblance to this condition. But the normal pulse rate makes it unlikely that these attacks were initiated by ventricular asystole due to disturbance in rhythm. Various authors have, perhaps for want of a better term, called these attacks epileptiform. Our patient was a mental deficient, and this would justify serious consideration of the possibility of epilepsy in his case, but the detailed description of the attacks fails to reveal any of the stigmata of epilepsy such as tonic and clonic phases, biting of the tongue, and salivary frothing at the mouth. Dr. Ramsay, who observed and described the episode of November 30, states "attack did not suggest epileptiform attack so much as cerebral engorgement."

Abbott[3] in her comprehensive work on congenital heart disease refers to "Syncopal and Epileptiform Attacks" in cases of tetralogy of Fallot. After mentioning two cases (one of which is our own) in which there was a high degree of polycythemia, she considers the pathological physiology of these symptoms in the following terms:

"It seems probable that the great viscosity of the blood which must have existed under these conditions may have introduced some cerebral factors such as thromboses in the capillary circulation, which may have combined with the anoxemia and high unsaturation to produce this remarkable picture."

Cases of polycythemia rubra vera have been reported in which cerebral symptoms varying from headache and attacks of slight dizziness to paralyses of arms and legs occurred. In the majority of such cases in which the brain was examined, thrombosis in the cerebral vessels was found. Christian[11] reports ten cases, in all of which cerebral symptoms occurred. The brain was examined in four cases that showed clinical signs of permanent damage to the brain tissues. In three of these, cerebral thromboses were found; in the fourth, arteriosclerosis and cerebral softening were present.

Thromboses were present in our case: the attacks of loss of consciousness, the transitory ankle and rectus clonus, incontinence, twitching of muscles, etc., may be related to small thromboses in various parts of the brain.

The first encephalopathic symptom was headache, first mentioned in the record of the patient's symptoms in April, 1923. Two months later he began to have brief spells of dizziness without loss of consciousness, and without any symptoms suggestive of epilepsy: these occurred only when he was in the erect posture, and they gradually increased in frequency so that within six months they occurred almost daily. In December, 1924, while he was in the hospital, the first attack of loss of consciousness occurred; it is noteworthy that this began when he was seated and that there was acute pulmonary edema and flaccid paralysis during this attack. During the year following this episode there were very frequent recurrences of loss of consciousness ushered in by dizziness; these attacks came on usually when he was in the erect posture and lasted about ten minutes. He was observed in one of these attacks while in the hospital, in November, 1925; he breathed stertorously and was more deeply cyanotic than usual during this period of unconsciousness, but no blood-stained froth was observed to ooze from the mouth. The history of the nature of his death—a suddent onset of one of his attacks of unconsciousness accompanied, however, by oozing of frothy blood from the mouth—is typical of pulmonary edema due to cardiac failure, such as is met with as a medical emergency in cases of mitral stenosis. Thus there was gradually progressive increase in the severity of the encephalopathic symptoms over a period of two and a half years. During this same period the efficiency of cardiac function progressively diminished, and there appears to be a direct relationship between the severity of the cerebral symptoms and the degree of cardiac failure. This suggests another approach to the elucidation of the mechanism responsible for the encephalopathic manifestations. The headache, dizziness and transitory spells of loss of consciousness resemble the syndrome induced by anoxemia which was described by Haldane.[7] Although our patient had a normal basal metabolism and was also able to accumulate an oxygen debt during slight exertion, the oxygen in his arterial and venous streams became rapidly diminished during exercise; the limits of his reserve were very narrow. The development of cardiac failure further impaired the efficiency of his circulation, so that one may suspect that anoxemia of the tissues occurred very readily during any physical strain. The fact that the attacks of dizziness and loss of consciousness at first appeared only when he was in the erect posture, and later even when he was lying down or sitting, and the association of some of these attacks with acute pulmonary edema, indicate the likelihood that they were initiated by transitory myocardial failure of a more or less profound degree, which led to cerebral anoxemia, the immediate cause of the symptoms.

The more severe attacks characterized by loss of consciousness, stertorous breathing, convulsive movements, constriction of the pupils followed

by marked dilatation, flaccid paralysis with loss of reflexes and incontinence of sphincters, bear a direct resemblance to the syndrome of asphyxia that may be produced experimentally in animals. Such attacks were usually accompanied by acute pulmonary edema, and it was in one of these attacks that he died.

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A METHOD FOR THE MEASUREMENT OF THE VELOCITY OF THE PULMONARY AND PERIPHERAL VENOUS BLOOD FLOW IN MAN*

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ALL methods used in the past for the measurement of the velocity of blood flow in man have consisted of the injection of a substance into a peripheral vein, and the determination of the time elapsing between the injection and the arrival of the substance at another designated point in the circulation. The time interval between injection and arrival of the fastest particle of blood through the designated portion of the circulation has been termed the circulation time for that particular pathway. The reliability of any method which employs this procedure depends primarily upon the accuracy with which the earliest traces of injected substances can be detected in the blood stream. The circulation time has been determined by: (1) The fluorescine method of Koch[1] in which the arrival time was indicated by the appearance of dye in the venous blood of the forearm. Technical difficulty in securing the necessary blood samples and in detecting the earliest traces of dye has made this method rather impracticable. (2) The conductivity method of Stewart[2] which made use of the change in electrical conductivity of the blood caused by the addition of an electrolyte. Strong sodium chloride solution was injected intravenously into animals, and its time of arrival registered through suitable electrodes and a sensitive galvanometer. Although sound in principle, and reliable in animals, its applicability in patients has not proved feasible in our experience. (3) Radium emanation has been employed successfully in estimating the velocity of blood flow.[3, 4, 5] A small nontoxic dose of radium emanation is injected intravenously, and its arrival at one or more points in the circulation is registered by a device sensitive enough to detect the early traces of radium. This method not only permits measurement of the circulation rate in the large blood vessels but makes possible a separate estimation of the rate of blood flow in the pulmonary and peripheral circulations. In this lies its chief significance. However, despite these advantages, the expense, the technical proficiency required by the method, and its bulkiness constitute serious disadvantages and restrict its use. The fact that measurement cannot be repeated within less than three hours is also a disadvantage for certain observations. (4) A new type of method was introduced by the use of pharmacological agents such as carbon dioxide, histamine, calcium

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chloride and others for measuring the circulation rate. The arrival of the injected substances is registered by a characteristic and readily discernible effect upon some physiological function. The time interval between the injection and the bodily reaction, the reaction time,* represents the circulation time from the site of injection to the responsive organ. It is essential that the signal reaction, upon which the accuracy of the reaction time largely depends, shall be objective, demand no cooperation on the part of the patient and shall occur promptly after arrival of the active agent in the reacting organ.

Because of failure to comply with one or more of these requirements the results of a number of pharmacological methods are of limited value. Bornstein[6] attempted to measure the circulation time by the inhalation of carbon dioxide. The time interval between the inspiration of carbon dioxide and the first deep respiration was thought to be an expression of the circulation time from the capillaries of the lung to the respiratory center. Because of variations in the response to carbon dioxide in pathological conditions, Bornstein himself recognized the limited applicability of the method. Loevenhart, Schlomowitz and Seybold[7] determined the circulation time in animals by injecting sodium cyanide intravenously. The resulting stimulation of respiration was used as an indication of the arrival of cyanide in the respiratory center. Although the circulation time by this method compared favorably with those obtained by ferrocyanide, hexamethylene and lithium chloride in the rabbit and dog, no application of it was made in man. The histamine method[8] depends upon the intense flush of face and neck caused by the arrival of histamine in the small blood vessels of the skin. A salty or metallic taste occurs simultaneously with the onset of the flush and serves as a verification of the arrival time of histamine. Headache following its use and its failure to produce an objective reaction in severe anemia and in dark-colored races limit its usefulness. In 1930 Kahler[9] employed calcium chloride for estimating the rate of blood flow in various parts of the body. He injected calcium chloride intravenously and made use of the sensation of heat which followed its course throughout the body in estimating the circulation time to the head and neck, hands, feet and buttocks. Although the results reported by Kahler are in fair agreement with the circulation time obtained with other reliable methods, the method must be limited in application because of the entirely subjective nature of the reaction. More recently Winternitz, Deutsch and Brüll[10] used decholin, a preparation of dihydrochloric acid which produces a sudden intensely bitter taste upon arrival in the mouth. This method, again, is subjective, dependent upon the intelligence and cooperation of the subject and, therefore, cannot be trustworthy in many pathological conditions.

*The term reaction time refers to the time interval between injection and reaction. It should not be confused with the term reaction time proper which is the period required for reaction to occur after arrival of the pharmacological agent in the reacting organ.

Each of the different methods for estimating the velocity of blood flow offers certain advantages, depending upon the nature of the inquiry; and each possesses limitations which must be considered in the selection of a method.

THE PROBLEM

In order to study sudden changes in the circulation in certain diseases a reliable method was needed for measuring at frequent intervals the rate of blood flow in man which could be used at the bedside with little delay, and preferably by one observer. None of the available methods met with these requirements. The conductivity method of Stewart,[2] as well as the modifications of Meldolesi[11] and Koch,[12] proved unsuitable. We were, therefore, forced to find a chemical substance which, through its pharmacological properties, might be satisfactory.

A chemical substance suitable for measurement of the velocity of blood flow in man should fulfill the following requirements: (1) It should be nontoxic in the dose employed. (2) It should not influence the velocity of blood flow until the signal reaction has occurred. (3) The substance and its effect on the body should be rapidly inactivated so that measurements may be repeated after short intervals of time. (4) The signal reaction of primary importance in the method must be objective and readily discernible in both normal and pathological conditions. It should be suitable for graphic registration. The reaction time proper of the substance after arrival in the reactive organ should be a negligibly small fraction of the entire reaction time which consists of circulation time plus reaction time proper.

The pharmacological studies of Loevenhart and his coworkers[13] on the effect of sodium cyanide suggested this substance as a suitable agent for measurement of the velocity of blood flow in man. They administered sodium cyanide intravenously to animals and man and found it to be a safe and effective stimulant of respiration when given in proper dosage. A latent period invariably occurred between the injection of cyanide and increased respiration, which suggested to them its use for measuring the circulation time of the blood. Although experiments in animals later demonstrated its exceptional qualification for this rôle,[7] cyanide was not used for measurement of the circulation time in man as far as can be ascertained.

The cyanide radical, although usually regarded as highly toxic, occurs normally in certain plants[14] and even in the animal body. Cyanide in the form of thiocyanate is a normal constituent of human saliva,[15] urine,[16] and gastric juice.[17]

Cyanide stimulates all of the medullary centers, but the most striking effect is upon respiration. Small doses cause an increase in the rate and amplitude of respiration, whereas toxic doses produce a fleeting stimulation, followed rapidly by shallow irregular breathing, and finally by a paralysis of respiration and death. According to Loevenhart[13] the respiratory stimulating dose of sodium cyanide in man, when injected

rapidly into the vein, is 3 to 5 mg., approximately 0.04 to 0.07 mg. per kg. of body weight; whereas the fatal dose of injected sodium cyanide in both animals and man was estimated to be about twenty times the respiratory stimulating dose. The toxicity of sodium cyanide is considerably lower than that of several of the glucosides and alkaloids employed in clinical medicine.[14] Cumulative effects do not readily occur from the therapeutic administration of cyanide because of its rapid inactivation in the body, which progresses, according to Loevenhart, at the rate of 1.5 to 2 mg. per minute in man. It is converted in part into relatively innocuous sulphur compounds, and in part into less closely related nitrogenous compounds. Excretion occurs as hydrocyanic acid on the breath and as cyanide and sulphocyanide in the urine.[18] These data on the pharmacology of the cyanide group clearly indicate that sodium cyanide can be safely administered to man intravenously in amounts to cause a distinct stimulation of respiration, and that this can be repeated after short intervals of time.

PLAN OF INVESTIGATION

In order to find out, in the first place, whether sodium cyanide could be safely administered to man in amounts adequate to cause distinct stimulation of respiration, it was administered intravenously in varying amounts to a large number of volunteer subjects, and its effect on respiration and circulation was observed.

In order to ascertain whether the reaction time of cyanide would be an accurate measure of the true circulation time and whether a practical application could be made clinically, the following observations were made. The reaction time of cyanide in normal subjects was compared with the circulation time obtained by the radium emanation and histamine methods. The constancy of the reaction time with varying doses of cyanide was investigated. Repeated estimations were made at short intervals to ascertain whether frequent determinations of the cyanide reaction time were feasible. For comparison of the results obtained by two methods under identical conditions, estimations of the circulation time by both the cyanide and the histamine methods were performed in the same individual. For a more precise evaluation, simultaneous determinations of the cyanide reaction time and glucose circulation time were made.

OBSERVATIONS ON THE EFFECT OF SODIUM CYANIDE IN MAN

The Dosage of Cyanide.—We found, as anticipated, that the greater the concentration of sodium cyanide and the smaller the volume of solution injected the more abrupt and intense was the respiratory stimulation. A 2 per cent aqueous solution of sodium cyanide (C. P. Merck), which permitted the rapid injection of an effective dose of cyanide in small volume without significant alteration in blood volume or velocity of blood flow, proved the most suitable concentration. The injections were made

rapidly from a graduated 1 c.c. Luer syringe into a large peripheral vein, usually the antecubital vein of the forearm, of resting subjects whose cooperation had been gained previously. Initial ineffective amounts of cyanide were gradually increased until a marked respiratory response was obtained. Later, however, only doses within the effective range for respiratory stimulation were administered.

The intensity of respiratory stimulation was, in general, proportional to the quantity of cyanide injected. Small amounts, such as 2 to 4 mg., caused indefinite respiratory reactions, whereas large doses, as 10 to 20 mg., produced intense dyspnea, labored breathing and tachycardia. The quantity of cyanide required to cause a moderately intense or optimal respiratory response varied considerably but was roughly proportional to body weight. In 35 normal* subjects the optimal dose of cyanide, when injected into the *antecubital vein* of the forearm, ranged from 5 mg. to 10 mg. corresponding to 0.25 to 0.5 c.c. of 2 per cent aqueous solution of sodium cyanide, or 0.07 mg. to 0.19 mg. per kg. of body weight. The average optimal dose was 7 mg. or 0.35 c.c. of 2 per cent solution, or 0.11 mg. per kg. of body weight.

The optimal dosage of sodium cyanide required for *jugular injection* was approximately two-thirds of the antecubital dosage. It varied from 3 to 6 mg., corresponding to 0.15 to 0.3 c.c. of 2 per cent solution of sodium cyanide, or 0.05 to 0.1 mg. per kg., with an average value of 4 mg., equivalent to 0.2 c.c. of 2 per cent solution, or 0.066 mg. per kg.

The quantity of cyanide required to cause an adequate respiratory reaction, however, may in certain instances differ by 100 per cent from the calculated dose. This is particularly true in pathological conditions with dyspnea in which smaller amounts of cyanide must be administered. The nature of the respiratory response and cyanide dosage in disease will be discussed in a later publication.

The range of safe effective dosage in normal subjects was found to be wide. Three times the optimal dosage of cyanide was administered without untoward reactions.

The Effect of Cyanide on Respiration.—The optimal intensity of respiratory response to cyanide was characterized by a sudden abrupt onset which interrupted the existing phase of respiration, rapid progression to maximal intensity of respiration, and prompt return to normal breathing. The amplitude of respiration invariably increased several fold, in striking contrast to the rate of respiration which was but little accelerated and occasionally slowed. The duration of increased respiration varied from 15 to 30 seconds in normal subjects, usually about 20 seconds. No unpleasant subjective responses accompanied optimal respiratory stimulation in normal subjects. The cyanide reactions caused respiratory discomfort only when maximal ventilatory responses were produced.

*The term normal refers to normal adults without disease, and to convalescent hospital patients who presented no evidence of circulatory, respiratory, hemic or metabolic disease at the time of observation.

The Effect of Cyanide on the Circulation.—Coincident with, or immediately after, the onset of increased respiration an acceleration of the heart rate of 10 to 15 beats per minute generally occurred which persisted from three to five minutes. Rarely the heart rate decreased.

Inactivation of Cyanide.—Precise observations on the rate of cyanide inactivation in man were not made. The observations, however, on the persistence of the effect of cyanide on respiration and circulation indicate that the effect is transient, lasting only a few minutes, and are in agreement with the rate of inactivation of sodium cyanide in man observed by Loevenhart.[13]

No accidents or undesirable systemic reactions have occurred in our experience with cyanide administration. Local pain of short duration has followed perivascular infiltration with cyanide, but in no instance has thrombosis or necrosis occurred. We believe that sodium cyanide can be administered to man within a wide range of dosage and cause clear-cut stimulation of respiration without unpleasant side effects or serious consequences.

THE REACTION TIME OF CYANIDE IN NORMAL SUBJECTS

All measurements of the cyanide reaction time were made in subjects who had been resting in the recumbent position for twenty minutes or until the heart rate and blood pressure were constant. For accurate results it was found essential to avoid excitement which was liable to follow venepuncture. To minimize this effect the sites of cyanide injection were anesthetized with novocaine. This is particularly important in sensitive areas such as the foot and neck. Venous stasis, when required for venepuncture, was released promptly, and a time interval allowed for adequate restoration of normal venous blood flow before injection. The arm in which the injection was made, rested at the level of the right auricle. Optimal amounts of sodium cyanide in 2 per cent solution, sufficient to produce unequivocal signal reactions, were then injected rapidly intravenously so that the duration of injection rarely exceeded 0.5 second.

An objective measure of the reaction time of cyanide was accomplished by the combined use of kymograph, pneumograph, signal magnet and time marker for automatic registration of the time of injection and the onset of the respiratory reaction. An example of such graphic registration of the reaction time is shown in Fig. 1. As subsequent observations showed that the reaction time measured with a stopwatch coincided with that obtained with graphic registration, the former simpler method was adopted as adequate in routine determinations.

To secure separate measurements of the pulmonary and peripheral venous circulation time two or more sites for subsequent injections were employed: (a) A peripheral vein of the forearm or the foot, depending upon the peripheral circulation to be studied. For reasons discussed subsequently, the circulation times from these sites of injection were called

TABLE I

THE ARM-TO-CAROTID REACTION TIME OF CYANIDE IN NORMAL SUBJECTS

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		VITAL CAPACITY		SODIUM CYANIDE OPTIMAL DOSAGE		NUMBER OF DETERMINATIONS	REACTION TIME	MAXIMAL VARIATION IN REACTION TIME	DIAGNOSIS
			SYSTOLIC	DIASTOLIC	OBSERVED	PER SQ. M.						
		PER MIN.	MM. HG	MM. HG	C.C.	C.C.	MG.	MG./KG.		SEC.	SEC.	
R. F.	15	96	110	60	4200	2530	5	0.08	2	9	0	Appendectomy, convalescent
W. D.	26	74	100	60	4600	–	6	0.08	2	10	0	Upper respiratory infection, convalescent
W. N.	18	94	120	80	4450	2550	6	0.07	2	12	1	Peptic ulcer, convalescent
D. C.	17	72	125	85	4300	2400	6	0.09	3	13	0	Upper respiratory infection, convalescent
F. F.	17	72	110	45	–	–	6	0.11	3	13	0	Neurosis
K. M.	26	100	120	80	5200	2770	8	0.11	2	13	1	No disease
R. R.	27	88	115	60	4100	2260	10	0.14	4	13	3	Peptic ulcer, convalescent
Q. V.	48	80	100	55	4800	2550	6	0.08	3	13	2	Amputation of leg, convalescent
J. R.	31	82	120	80	4200	2470	8	0.13	4	14	1	Neurosis
H. D.	35	60	135	85	4550	2460	8	0.12	2	14	2	Neurosis
M. C.	45	84	120	75	3800	2090	8	0.11	2	14	1	No disease
H. S.	46	70	120	80	3800	2140	6	0.09	2	14	0	Pneumonia, convalescent
E. C.	50	84	125	80	3500	1900	6	0.13	2	14	1	Peptic ulcer, convalescent
W. T.	21	72	110	70	4500	2510	6	0.09	1	15	–	Atrophic arthritis, convalescent
M. B.	24	96	120	75	4500	2840	6	0.11	2	15	0	No disease
C. D.	25	82	110	65	4300	2330	5	0.08	2	15	0	Amputation of leg, convalescent
J. M.	48	84	155	85	3600	2130	6	0.10	1	15	0	Infectious arthritis, convalescent
J. P.	17	66	90	55	4200	2320	8	0.12	3	16	1	Tonsillitis, convalescent
J. K.	21	76	130	75	3900	2280	8	0.13	2	16	2	Vincent's angina, convalescent

TABLE I—CONTINUED

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		VITAL CAPACITY		SODIUM CYANIDE OPTIMAL DOSAGE		NUMBER OF DETERMINATIONS	REACTION TIME	MAXIMAL VARIATION IN REACTION TIME	DIAGNOSIS
			SYSTOLIC	DIASTOLIC	OBSERVED	PER SQ. M.						
		PER MIN.	MM. HG	MM. HG	C.C.	C.C.	MG.	MG./KG.		SEC.	SEC.	
F. W.	32	76	115	75	4800	2640	6	0.09	1	16	–	Upper respiratory infection, convalescent
A. K.	42	60	140	80	–	–	6	0.11	2	16	2	Neurosis
J. L.	44	78	105	75	–	–	6	0.13	3	16	1	Diabetes mellitus, mild
S. G.	17	72	110	65	4500	2340	10	0.14	2	17	0	Neurosis
P. M.	25	74	115	60	–	–	6	0.09	5	17	1	Cervical adenitis, convalescent
E. L.	28	88	125	80	–	–	8	0.12	2	17	2	No disease
M. T.	37	80	115	70	3200	2040	10	0.19	2	17	0	Tonsillitis, convalescent
R. D.	60	68	120	70	3100	1980	6	0.12	4	17	2	Hypertrophic arthritis, improved
O. T.	25	76	125	60	4000	2270	6	0.10	2	18	2	No disease
J. R.	25	66	120	65	–	–	5	0.08	2	18	1	Upper respiratory infection, convalescent
H. J.	27	76	120	80	6200	3000	10	0.14	1	18	–	No disease
C. D.	25	86	105	65	–	–	6	0.12	2	19	1	Pleurisy, convalescent
W. S.	31	84	120	85	5200	2610	7	0.11	2	20	2	No disease
R. G.	32	80	130	85	5800	3100	6	0.09	2	20	1	No disease
J. S.	41	84	145	85	3300	1990	10	0.17	1	20	–	Pneumonia, convalescent
J. D.	36	78	110	75	4300	2390	8	0.12	5	21	4	Burn, convalescent
Average	31	79	119	72	4320	2400	7	0.11	2	15.6	1	

the arm-to-carotid or foot-to-carotid circulation time. (b) The external jugular vein. This gave a measure of the crude pulmonary circulation time but included a short peripheral venous pathway. By difference the venous velocity index was derived, thus providing a practical estimation

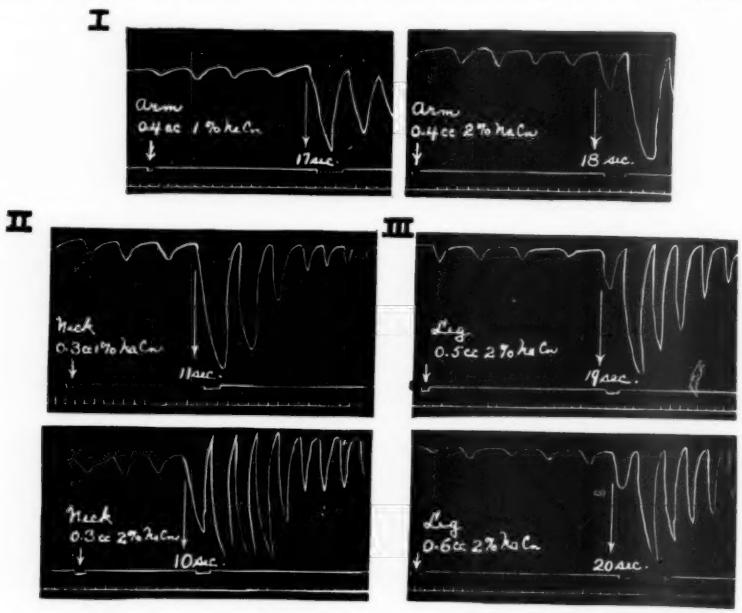

Fig. 1.—Graphic registration of the cyanide circulation time in subject P. M. I Arm-to-carotid circulation time. II Crude pulmonary circulation time. III Foot-to-carotid circulation time.

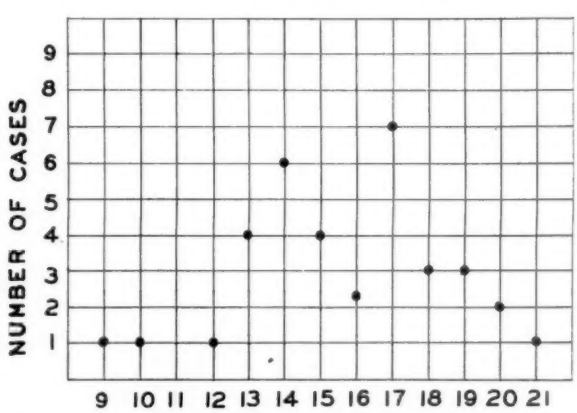

Fig. 2.—The arm-to-carotid circulation time in seconds, in 35 normal subjects.

of the velocity of venous blood flow, but not an exact measure of the circulation time from the point of injection to the right side of the heart.

The arm-to-carotid circulation time (antecubital injection) was determined in 35 normal subjects. In 21 of the 35 subjects the crude pulmonary circulation time (jugular injection) was also estimated. The arm-to-ca-

rotid reaction times and other observations are presented in Table I. The cyanide reaction time varied between 9 and 21 seconds; the average reaction time was 15.6 seconds. These values are in harmony with those obtained by the radium emanation method[4] in normal subjects in which the average arm-to-arm time was 17.5 seconds. It is of interest that the distribution of the cyanide reaction times (Fig. 2) is also similar to that obtained by the radium emanation method. The arm-to-carotid reaction time, the crude pulmonary circulation time, and the peripheral arm venous velocity index together with other observations are presented in Table II. The average heart rate, blood pressure, and vital capacity support the contention that the findings on the velocity of blood flow were measured under adequately normal conditions. The average crude pulmonary circulation time was 10.6 seconds, ranging from 7 to 14 seconds. The distribution curve is shown in Fig. 3. Here again, both average and extreme values and

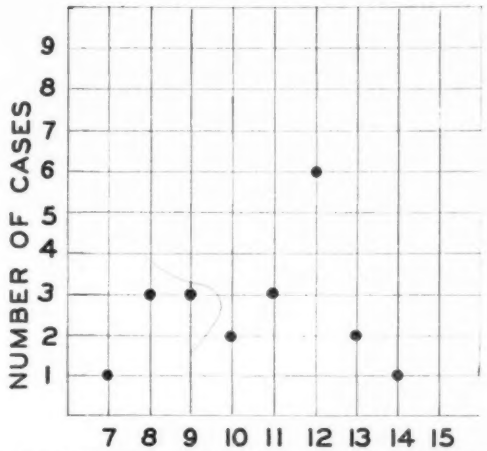

Fig. 3.—Crude pulmonary circulation time in seconds in 21 normal subjects.

character of distribution are in agreement with the crude pulmonary circulation times obtained by the radium emanation method.[5]

The index of venous velocity, which is derived by subtracting the crude pulmonary circulation time from the arm-to-carotid circulation time, expresses the circulation time for approximately three-quarters of the venous pathway from antecubital vein to heart, not the entire arm-to-heart circulation time. The venous circulation time, according to observations with the radium emanation method, is more variable and of less significance than the pulmonary circulation time. The same is true in this study. The individual measurements (Table II) ranged from 1 to 9 seconds. The average venous velocity index for the 21 subjects was 4.5 seconds. These results are in accord with those of the radium emanation method in which the average arm-to-heart circulation time was 6.6 seconds. If allowance be made for the shorter pathway represented by the venous velocity index, the results obtained with these methods become almost identical.

TABLE II

THE ARM-TO-CAROTID AND CRUDE PULMONARY REACTION TIMES IN NORMAL SUBJECTS

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		VITAL CAPACITY		SODIUM CYANIDE OPTIMAL DOSAGE		REACTION TIME		VENOUS VELOCITY INDEX	DIAGNOSIS
			SYSTOLIC	DIASTOLIC	OBSERVED	PER SQ. M.	ARM TO CAROTID	CRUDE PULMONARY	ARM TO CAROTID	CRUDE PULMONARY		
		PER MIN.	MM. HG	MM. HG	C.C.	C.C.	MG./KG.	MG./KG.	SEC.	SEC.	SEC.	
W. N.	18	94	120	80	4450	2550	0.07	0.05	12	7	5	Peptic ulcer, convalescent
F. F.	17	72	110	45	–	–	0.11	0.07	13	8	5	Neurosis
J. P.	17	66	90	55	4200	2320	0.12	0.09	16	9	7	Tonsillitis, convalescent
J. K.	21	76	130	75	3900	2280	0.13	0.08	16	9	7	Vincent's angina, convalescent
O. T.	25	76	125	60	4000	2270	0.10	0.07	18	9	9	No disease
W. D.	26	74	100	60	4600	–	0.08	0.06	10	9	1	Upper respiratory infection, convalescent
M. C.	45	84	120	75	3800	2090	0.11	0.06	14	9	5	No disease
D. C.	17	72	125	85	4300	2400	0.09	0.06	13	10	3	Upper respiratory infection, convalescent
E. C.	50	84	125	80	3500	1900	0.13	0.07	14	10	4	Peptic ulcer, convalescent
W. T.	21	72	110	70	4500	2510	0.09	0.06	15	11	4	Atrophic arthritis, convalescent
P. M.	25	74	115	60	–	–	0.09	0.05	17	10	7	Cervical adenitis, convalescent
H. S.	46	70	120	80	3800	2140	0.09	0.05	14	11	3	Pneumonia, convalescent
F. W.	32	76	115	75	4800	2640	0.09	0.06	16	11	5	Upper respiratory infection, convalescent
S. G.	17	72	110	65	4500	2340	0.14	0.08	17	12	5	Neurosis
C. D.	25	82	110	65	4300	2330	0.08	0.05	15	12	3	Amputation of leg, convalescent
H. D.	35	60	135	85	4550	2460	0.12	0.08	14	12	2	Neurosis
J. M.	48	84	155	85	3600	2130	0.10	0.07	15	12	3	Atrophic arthritis, convalescent
J. R.	31	82	120	80	4200	2470	0.13	0.10	14	12	2	Neurosis
R. G.	32	80	130	85	5800	3100	0.09	0.05	20	13	7	No disease
R. D.	60	68	120	70	3100	1980	0.12	0.06	17	13	4	Chronic arthritis, improved
J. R.	25	66	120	65	–	–	0.08	0.07	18	14	4	Upper respiratory infection, convalescent
Average	30	75	119	71	4220	2335	0.103	0.066	15.1	10.6	4.5	

TABLE III

VENOUS CIRCULATION TIME OF ARM AND LEG

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		SODIUM CYANIDE PER KG.			CYANIDE REACTION TIME			VENOUS VELOCITY INDEX		DIAGNOSIS
			SYSTOLIC	DIASTOLIC	ARM	FOOT	NECK	ARM TO CAROTID	FOOT TO CAROTID	CRUDE PULMONARY	ARM	LEG	
		PER MIN.	MM. HG	MM. HG	MG.	MG.	MG.	SEC.	SEC.	SEC.	SEC.	SEC.	
R. D.	60	68	120	70	0.12	0.16	0.06	17	29	13	4	16	Hypertrophic arthritis
E. C.	50	84	125	80	0.13	0.21	0.07	14	27	10	4	17	Peptic ulcer
J. Mc.	67	96	150	80	0.06	0.10	0.04	19	24	14	5	10	Arteriosclerosis
Q. F.	49	80	100	65	0.09	0.17	0.07	17	20	11	6	9	Neurosis
T. K.	48	72	140	85	0.10	0.16	0.07	18	29	12	6	17	Peptic ulcer
P. M.	25	74	115	60	0.09	0.15	0.05	17	19	10	7	9	Adenitis
R. G.	32	80	130	85	0.09	0.18	0.05	20	25	13	7	12	Normal
J. K.	45	72	130	70	0.10	0.17	0.07	22	30	13	9	17	Inactive pulmonary tuberculosis
A. R.	57	66	150	70	0.08	0.16	0.06	22	34	14	8	20	Arteriosclerosis
F. E.	62	72	160	100	0.09	0.16	0.08	24	40	16	8	24	Lead poisoning, convalescent
Average					0.09	0.16	0.06	19.0	27.7	12.6	6.4	15.1	

This method for estimating the velocity of venous blood flow can be employed in other regions of the body. To demonstrate the feasibility of this application of the cyanide method we have estimated the venous circulation time in both arm and leg in 10 individuals.

The venous circulation time of the arm was determined in the usual manner. The venous circulation time of the leg was obtained by injection into a dorsal vein of the foot. The dosage of cyanide required for the foot injection was found to be approximately 1.5 times the amount effective when injected in the arm. This difference in dosage is distinctly less than that with the histamine method. The leg circulation time was considerably longer than the arm circulation time (Table III), as shown by the average value of 15.1 seconds and 6.4 seconds, respectively. This difference is explained by the longer venous pathway from the foot to the heart.

By estimating the reaction time at different levels in the same venous pathway the circulation time for the designated portion can be ascertained. Such a differential estimate of the velocity of blood flow in various portions of the venous system may be of aid in a number of diagnostic problems. This procedure was undertaken in one subject who had many varicose leg veins. Consecutive injections were made into a dorsal vein of the foot, the great saphenous vein at the knee and the femoral vein at the groin. The reaction times were 46, 28, and 12 seconds, respectively.

A Comparison of the Results Obtained by the Radium, Histamine and Cyanide Methods.—To confirm the reliability of the cyanide method we have compared our results with those of the histamine as well as the radium emanation methods. The histamine method affords a measure of the circulation time from the arm to the small blood vessels of the face and brain; whereas the radium method measures the circulation time from the antecubital vein of one arm to the large brachial artery of the opposite arm, a pathway more clearly defined and less subject to variation. The pathways, therefore, differ fundamentally in character and in length. This is reflected in the difference in circulation time obtained with the two methods. The histamine reaction time, because of the peripheral location of its site of reaction, is consistently longer than the arm-to-arm circulation time of the radium method.

The results obtained with each method and the vascular pathways used are presented in Table IV. There is practical agreement throughout between the results obtained with the radium and cyanide methods, indicating that in normal subjects the reaction time to cyanide is a trustworthy measure of the circulation time. The longer average histamine reaction time of 23 seconds, however, contrasts strikingly with the cyanide reaction time of 15.6 seconds. Although a somewhat shorter reaction time had been anticipated because of the possibly greater rapidity of action of cyanide, such divergence between the results obtained with methods employing pathways regarded as essentially the same required explanation.

To verify the existence of a significant difference between the reaction time obtained with the two pharmacological methods we estimated the reaction time of both cyanide and histamine in 8 subjects under identical conditions but not simultaneously. These observations, which are recorded in Table V, clearly show that in the same individual the cyanide reaction time was, without exception, shorter than that of histamine. The difference varied from 4 to 9 seconds with an average difference of 6.5 seconds, which is of sufficient constancy and magnitude to indicate an essential difference in the vascular site of reaction.

TABLE IV

COMPARISON OF CIRCULATION TIMES IN NORMAL SUBJECTS DETERMINED BY THE RADIUM EMANATION, CYANIDE AND HISTAMINE METHODS

VASCULAR PATHWAY	RADIUM EMANATION METHOD		CYANIDE METHOD		HISTAMINE METHOD	
	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE
	SEC.	SEC.	SEC.	SEC.	SEC.	SEC.
Arm to heart	6.6	2-14				
Arm peripheral venous			4.5	1-9		
Crude pulmonary	10.8	5-17	10.6	7-14		
Arm to arm	17.5	14-24				
Arm to carotid			15.6	9-21		
Arm to face					23	13-30

TABLE V

COMPARISON OF HISTAMINE AND CYANIDE CIRCULATION TIMES IN THE SAME INDIVIDUAL

NAME	AGE	DIAGNOSIS	HISTAMINE REACTION TIME ARM TO FACE	CYANIDE REACTION TIME ARM TO CAROTID	DIFFERENCE
	YEARS		SEC.	SEC.	SEC.
C. D.	25	Amputation of leg	22	15	−7
R. R.	27	Neurosis	19	13	−6
M. T.	37	Tonsillitis	23	17	−6
Q. V.	48	Amputation of leg	18	12	−6
E. C.	50	Peptic ulcer	19	13	−6
J. M.	56	Cholecystitis	28	20	−8
R. D.	60	Arthritis	26	17	−9
P. R.	57	Arteriosclerosis	18	14	−4
Average			21.6	15.1	−6.5

Histamine is known to exert its dilator action directly upon the minute vessels of the skin and the brain. The flush is due mainly to its primary action on the small veins. The reaction time of histamine, therefore, is the time required for the blood to flow to the subpapillary venules rather than to a more proximal point of the large arteries, as is the case with the radium

method. We have, previously, attributed the prolonged reaction time of the histamine method to a considerable slowing of blood flow in the smaller vessels. Hering[19] estimated the capillary circulation time to be 5 seconds; according to Koch's observations[1] the capillary time would correspond to 8 seconds in man. Similarly, in this laboratory, study of capillaries by direct observation showed the rate of blood flow to be slow.

In contrast to histamine our knowledge of the site of action of cyanide in man is meager. The increase in respiration caused by its administration has been assumed to be due to the direct action of cyanide on the respiratory center. This would require that cyanide must also be delayed in arriving at the respiratory center, because of the similarity in blood supply and circulation time to the skin of the face and the brain.[8] Thus, unless there is a considerable difference in the rapidity of action of these two substances after their arrival in the capillaries of the brain, their reaction time should be in close agreement. Since the large difference of 6.5 seconds between the two methods cannot be ascribed to a more rapid action of cyanide after its arrival, it must be explained by a shorter pathway and circulation time of the blood to the site of cyanide action. Such a postulation would exclude the respiratory center as the site of cyanide stimulation of respiration.

The recent investigations of Heymans, Bouckaert and Dautrebande,[20] confirmed by Owen and Gesell,[21] have thrown new light on the mechanism of the action of cyanide on the respiration. By denervation experiments in animals these investigators demonstrated conclusively that sodium cyanide exerts its action predominantly upon the carotid sinus, a portion of the common carotid artery near the bifurcation and in contact with the respiratory center through afferent nerves; and that sodium cyanide has little or no effect directly upon the respiratory center. They further observed that the stimulation of respiration occurred instantaneously after the injection of cyanide into the common carotid artery. According to this evidence the reaction time to cyanide is the time required for blood to flow to the carotid sinus of the carotid artery. This provides a rational explanation for the shorter reaction time of the cyanide method, and also its correspondence with the results obtained with the radium emanation method.

Since the action of cyanide on the carotid sinus of man has not been demonstrated, we resorted to indirect methods to throw additional light on the mechanism of cyanide action in man.

In order to ascertain whether or not the cyanide reaction time corresponds to the time required for the blood flow to reach the carotid artery, the cyanide reaction time and the actual circulation time were determined simultaneously in 7 individuals. An adequate amount of sodium cyanide, dissolved in 5 c.c. of a 50 per cent glucose solution was injected rapidly into the antecubital vein of the arm and the circulation times of both the cyanide and the glucose were determined. The usual method of register-

ing the reaction time of cyanide was used. The circulation time of glucose was determined by its appearance in the arterial blood, as shown in blood samples obtained from the femoral artery at known intervals of time. In each case satisfactory estimations of both circulation times were obtained similar to those reported for subject M. I. in Fig. 4. The results for the

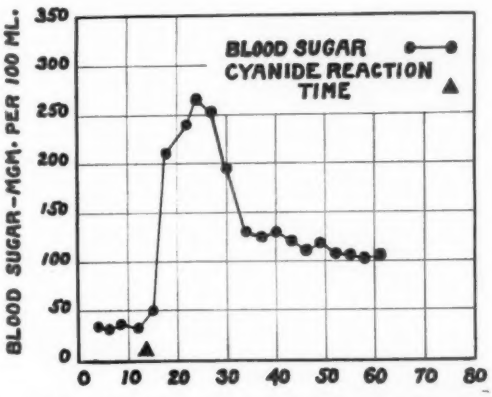

Fig. 4.—Simultaneous determinations of the arm-to-femoral glucose circulation time and arm-to-carotid cyanide reaction time in seconds, in subject M. I.

TABLE VI

COMPARISON OF CIRCULATION TIMES DETERMINED SIMULTANEOUSLY BY THE GLUCOSE AND CYANIDE METHODS

NUMBER	NAME	AGE	DIAGNOSIS	GLUCOSE CIRCULATION TIME ARM TO FEMORAL	CYANIDE CIRCULATION TIME ARM TO CAROTID	DIFFERENCE
				SEC.	SEC.	SEC.
1	H. S.	46	Pneumonia, convalescent	11	13	+2
2	M. R.	49	Arteriosclerosis	14	14	0
3	M. I.	49	Arteriosclerosis, hypertensive heart disease	15	13	−2
4	F. P.	62	Hypertensive heart disease	19	17	−2
5	R. M.	62	Hypertensive heart disease	25	23	−2
6	P. F.	68	Arteriosclerotic heart disease decompensation	26	24	−2
7	J. F.	49	Luetic heart disease decompensation	28	25	−3
			Average	19.7	18.4	−1.3

seven subjects are summarized in Table VI, and show remarkably close agreement of the reaction time of cyanide and the circulation time of the blood to the femoral artery. In the majority of subjects the circulation time of the blood to the femoral artery was slightly longer than the cyanide reaction time. The average prolongation of 1.3 seconds corresponds closely

to the longer arterial circulation pathway of the blood to the femoral artery than to the carotid artery. This difference of 1.3 seconds is the more significant, as opening of the femoral artery should theoretically increase the velocity of blood flow in that vascular area. The close agreement then between the reaction time of cyanide and the circulation time to the femoral artery we accept as substantial, although indirect, evidence that in man as well as in animals sodium cyanide acts upon the carotid sinus. Thus the cyanide reaction time measures the velocity of blood flow between an arbitrarily chosen vascular area and a large artery, as does the radium emanation method. It may also be concluded from the close agreement of reaction time and circulation time in man, as well as by animal experiment,[20] that cyanide provokes an immediate increase of respiration upon arrival in the carotid sinus; and that the time required for cyanide to act after arrival must be a negligibly small part of the total reaction time. This state of affairs makes sodium cyanide a particularly adaptable substance for the measurement of the velocity of blood flow.

The Effect of Dosage on the Reaction Time.—A delay in the occurrence of the respiratory response to cyanide was observed whenever only slightly effective doses of cyanide were used. To find out whether the reaction time of cyanide varied with the dosage, it was administered in amounts to cause varying degrees of response, and the reaction time to each was determined. A suboptimal response was usually associated with a prolongation of reaction time varying from 3 to 10 seconds; whereas, with all doses sufficient to call forth an abrupt, definite stimulation of respiration, the reaction

TABLE VII

THE EFFECT OF DOSAGE ON THE REACTION TIME OF CYANIDE (SUBJECT R. G.)

TIME OF DETERMINATION	HEART RATE	SODIUM CYANIDE INJECTED	REACTION TIME	INTENSITY OF REACTION
	PER MIN.	MG.	SEC.	
1:36 P.M.	76	2	...	0
1:40	76	4	...	0
1:46	76	5	22	1+
1:51	78	6	18	2+
2:06	76	7	17	2+
2:15	78	8	16.5	3+
2:22	76	9	16	3+
2:32	76	10	16	4+
2:46	78	12	16	4+

times were remarkably constant. The results obtained in one of numerous experiments are presented in Table VII. The dose of 5 mg. (0.07 mg. per kg.) produced only a mild reaction occurring 22 seconds after injection; whereas 7 mg. caused a satisfactory reaction with a reaction time of 17 seconds which was not altered significantly with larger doses, although the intensity of reaction was increased. Thus, the reaction time of cyanide is

significantly affected by the dosage only when amounts are employed that do not give clear-cut, sudden respiratory reactions.

Repeated Estimations of the Reaction Time to Cyanide.—In order to ascertain beyond doubt the feasibility of employing the cyanide method at frequent intervals, repeated estimations were made of the reaction time of cyanide at close intervals of time in eight normal subjects. In each instance an optimal quantity was administered, and the heart rate was permitted to return to normal before subsequent injections were given. The number of determinations, as indicated in Table VIII, varied from 3 to 8 for each subject, and the time intervals between injections from 4 to 19 minutes. The reaction times in the same individual agreed as a rule within 2 seconds. In subjects J. D., R. R., and J. R. the maximal difference of 3

TABLE VIII

REPEATED DETERMINATIONS OF THE REACTION TIME OF CYANIDE

NAME	AGE	DIAGNOSIS	HEART RATE	NUMBER OF DETERMINATIONS	AVERAGE TIME INTERVAL BETWEEN DETERMINATIONS	RANGE OF REACTION TIME
			PER MIN.		MIN.	SEC.
J. P.	17	Tonsillitis, convalescent	66	3	10	15-16
Q. V.	48	Amputation of leg	80	3	4	12-14
J. L.	44	Diabetes	78	3	8	16-17
R. D.	60	Arthritis	68	4	6	16-18
P. M.	25	Adenitis, convalescent	70	5	12	17-18
J. D.	36	Burn, convalescent	78	5	13	18-22
R. R.	27	Peptic ulcer	88	7	19	9-13
J. R.	31	Neurosis	82	8	11	13-16

to 4 seconds was associated with restlessness which occurred after frequent repetitions of the test. The time intervals represented here do not express the shortest interval possible between estimations, for no attempt was made to estimate this aspect precisely. We have, however, observed frequently that the estimation of the cyanide reaction time can be repeated satisfactorily at 3 to 5 minute intervals provided that the heart rate has returned to normal before subsequent estimations are made.

DISCUSSION

In outlining the problem of this investigation it was stated that the cyanide method, in order to be suitable for measuring the velocity of blood flow in man, should fulfill certain prerequisites. In the light of our experience cyanide fulfills these requirements in the following manner:

In repeated observations no serious effects followed its administration intravenously. A wide range of effective but safe dosage of sodium cyanide exists, sufficiently removed from the dangerous dose to warrant its use in man.

Cyanide does not influence the velocity of blood flow during the first circulation of the blood after injection until the respiratory response has occurred. This is supported by the absence of any change in the heart rate, pulse or arterial blood pressure prior to the occurrence of increased respiration.

The inactivation of cyanide and the disappearance of its effect progress rapidly in the body. The more pronounced stimulation of respiration is fleeting, lasting for only several seconds, whereas the increase in heart rate, although of longer duration, rarely persists more than a few minutes. In the average normal person, the effect of cyanide has disappeared in 3 to 5 minutes, so that the administration may then be repeated.

The change in respiration caused by cyanide is eminently suited for the rôle of signal reaction. The abrupt onset and conspicuous increase in amplitude occur at any phase of the normal respiratory cycle and can be promptly detected and accurately registered either by graphic registration or by stopwatch.

The time elapsing between the arrival of cyanide and ensuing increase in respiration is a negligibly small fraction of the entire reaction time of cyanide. The unusual sensitivity of the respiratory mechanism to cyanide, the abrupt nature of the reaction and, most important, the close agreement between circulation time and reaction time leave little room for doubt that reaction occurs immediately after arrival of cyanide in the carotid sinus.

The simplicity of the cyanide method, which requires only a syringe, cyanide solution and stopwatch, makes possible its prompt application by one person in practically any position or condition in which the subject may be. Additional observations during exercise in this laboratory,[22] and in pathological conditions,[23] confirm the feasibility of its use under a variety of conditions.

The reliability of the reaction time as an accurate measure of the circulation time in large vessels has been demonstrated by the agreement between the results obtained with the cyanide method and with the radium emanation and glucose methods known to exclude the circulation time in small vessels. Additional evidence concerning the cyanide pathway has been provided by the consistent disagreement with the histamine method known, on the other hand, to include the circulation time in small blood vessels. According to this evidence the cyanide method measures the circulation time to a large artery, which would imply that the respiratory stimulation is initiated in or near a large vessel. The close correspondence between the reaction time of cyanide and the circulation time of the blood to the carotid artery lends support to this thesis, and is consistent with the location of the site of cyanide action in the carotid sinus in man.

Separate estimations of the venous and pulmonary circulation times have been feasible with the cyanide method, and the accuracy of these measurements verified by comparison with the radium emanation method.

The cyanide method measures the pulmonary circulation time between the jugular vein and the carotid artery in man, which is the identical pathway measured in animals by Stewart[24] with the aid of his conductivity method. The application of the cyanide method for measuring the venous circulation time in various regions of the body and in the various portions of the same vessel has been described, and the feasibility demonstrated by studies in normal subjects.

SUMMARY AND CONCLUSIONS

1. Sodium cyanide in amounts sufficient to stimulate respiration has been injected intravenously in thirty-five normal individuals, and the effects on the circulation and respiration have been observed.

2. The optimal dose of cyanide varied with the weight of the subject and with the site of injection. The average optimal dose for injection into the antecubital vein was 7 mg., corresponding to 0.35 c.c. of 2 per cent solution of sodium cyanide or 0.11 mg. per kg. With jugular vein injections a comparable effect was obtained with approximately two-thirds of the antecubital dose. For foot injection, one and one-half times the antecubital dose were required.

3. The time elapsing between injection and the occurrence of increased respiration corresponded closely to the circulation time.

4. A simple method that registers the circulation time graphically and automatically is described.

5. Two sites of injection were used for measurement of pulmonary and peripheral venous circulation times: (1) The external jugular vein of the neck which measures the pulmonary circulation time; (2) the antecubital vein of the forearm or a superficial vein of the foot which measures the arm-to-carotid or foot-to-carotid circulation time. By difference the arm or leg venous circulation time is derived.

6. The average arm-to-carotid circulation time in thirty-five normal subjects was 15.6 seconds; it varied between 9 and 21 seconds. The average jugular-to-carotid or "crude pulmonary circulation time" in twenty-one subjects was 10.6 seconds, ranging from 7 to 14 seconds. The average arm index of venous velocity was 4.5 seconds. In 10 individuals the venous circulation time from the foot was found to be 15.1 seconds.

7. The reliability of the reaction time of cyanide as a measure of the velocity of the blood flow has been shown by the remarkably close agreement with the circulation times obtained with the radium emanation and glucose methods.

8. The reaction time of cyanide was constant when sudden clear-cut respiratory reactions were obtained, even though their intensity varied considerably.

9. Repeated estimations of the circulation time with cyanide were feasible after such short intervals as 3 to 5 minutes. Repeated estimations varied 2 seconds or less.

10. Evidence is presented that cyanide exerts its action upon the carotid sinus in man.

11. The cyanide method is a simple, reliable and objective method for estimating the velocity of blood flow of the various circulatory pathways of man.

We wish to express our appreciation to Dr. Benedict F. Massell for his assistance in this study.

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A METHOD FOR OBTAINING BLOOD PRESSURE BY ARTERIAL COMPRESSION AND SIMULTANEOUS CAPILLARY OBSERVATION*

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THE ordinary methods for obtaining blood pressure readings in man are dependent upon detection of a pulsation either by palpation, auscultation, or by recording instruments. In the occasional case in which there is no pulsation the only method available is direct cannulization or needling. Although needling, that is, arterial puncture, can be done with impunity by the experienced, in the hands of the inexpert it may involve considerable pain and even a slight risk of local damage. It should also be noted that the operator usually locates the brachial artery by palpation before inserting the needle. When there is no pulsation, this guide is lost and the difficulty of the procedure is increased.

In 1930 a patient of Dr. Francis Grant was admitted to the University Hospital on the neurosurgical service of Dr. C. H. Frazier, and subsequently transferred to the ward of the medical clinic. This man presented a number of interesting clinical features which will be reported separately by Drs. M. Bowie and L. H. Collins. For the purpose of this communication it is sufficient to state that he was a man aged forty-two years with aneurysm of the aorta presumably luetic, a blood pressure in the legs varying between 216-162 systolic and 100-44 diastolic, and a complete absence of pulsation in the neck or upper extremities. In addition, he was subject to curious cerebral attacks, at times consisting of blindness, at times of syncope, and at times of actual convulsions. Considerable interest centered around the question of the blood pressure in the arms, which could not be obtained by the usual methods. One of us (J. Q. G.) was at that time making certain clinical capillary studies in connection with another problem, and it was suggested he study this patient. Accordingly a series of observations were begun which were interrupted by the patient's departure from the hospital. The principle employed in these first observations was that the brachial artery was occluded by the blood pressure cuff when capillary flow could not be seen, and was not occluded when flow could be seen. This was in agreement with the work of E. Weiss.[1] It was not realized at that time, however, how long the flow in the minute vessels could continue after brachial occlusion. Subsequently the method was perfected, using normal subjects, so that when the patient returned to the hospital in 1932 it was possible to repeat the observation, this time

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with consistent and satisfactory results. After readings had been obtained by this indirect method, one of us (L. H. C., Jr.) secured a direct reading by puncture of the brachial artery.

Method: A microscope lamp with a 500-watt bulb is set up so that its rays fall on the stage of a microscope at an angle of 45°. A spherical liter flask filled with distilled water is interposed between the lamp and the stage, serving to absorb heat and also acting as a lens to concentrate the light at the center of the stage. An ordinary microscope is used with a 5 ocular and a 32 objective. On the side of the microscope opposite to the lamp pillows are placed to support the patient's arm. One of the patient's fingers, usually the fourth, is inserted into a small wooden box. This box is shaped like a trough, with high sides but cut down ends. The finger is gently supported on the sides by plasticine and the box placed directly on the stage, with the arm resting on the pillows. A drop of immersion oil is then placed on the selected finger just back of the nail, and observation is begun.

The area chosen is that just back of the limbus where invariably one sees at least one row of hairpin shaped capillaries coursing parallel to the skin. If this area has been destroyed and observations must be made on more proximal capillaries where only the tips are visible, the procedure is much more difficult. A detailed description of the usual capillary bed has been taken up in a previous article.[2]

It is most important to select capillaries favorable for observation. At this magnification individual red blood cells cannot be seen, and most of the capillaries show as solid red bands. The phenomenon to look for is that commonly known as "granular streaming," which is shown when groups of red cells, usually five to ten in number, sweep along in clumps. When this is not present, blood flow is practically indetectable. Granular streaming is normally present in a few capillaries, but it can be readily produced in many capillaries by placing a blood pressure cuff about the arm and pumping it up to thirty or forty millimeters of mercury pressure. Capillaries which show granular streaming under these conditions will also show it under the conditions of the actual determination, and may therefore be regarded as suitable. It should be stated that the large red capillaries are usually the poorest for observation, for in them the cells are clumped and the flow is sluggish. Also, the best place to observe motion is at the junction of the arterial with the intermediate portion of the loop, that is, just at the arterial side of the tip. After a suitable capillary or capillaries have been selected, the finger box is moved so that the desired area is in the center of the field. If the armlet cuff has been partially inflated, it should be completely deflated and a rest of at least two minutes allowed.

It is now time to take the actual reading. The blood pressure cuff is quickly pumped up to a point above systolic pressure and clamped while the capillaries are watched. Ordinarily flow will continue for about a minute, perhaps a little more or a little less; and then certain of the capillaries, especially those which previously showed granular streaming, will appear to be filled with stagnant granules. If the flow does not stop, it means that a point above systolic pressure has not been reached. There may be slight to and fro movements of the granules, but there should be no definite stream. Many of the capillaries, of course, continue to maintain the appearance of solid red bands.

The pressure in the cuff is now slowly lowered, and the point where flow first definitely returns is read on the manometer. This is taken as systolic pressure. For the first reading it is well to lower the pressure slowly but steadily so as not to take too much time and cause the patient too much discomfort. Thus an approximate reading is obtained, which is too low. Then, after a few minutes' rest the procedure can be repeated, this time raising the pressure to twenty millimeters above the approximate

reading, waiting for cessation of flow, and then dropping it very slowly, so as to obtain as accurate a reading as possible. When properly done, the end point is very clear and definite.

SOURCES OF ERROR

If the nail beds have been traumatized, as by manicuring, the procedure is difficult because the most favorable areas for observation have been destroyed. In negroes the method is impossible because of the pigment. Observation is difficult in those with marked tremor. This may be corrected to some extent by strapping the box to the stage with adhesive tape.

It is theoretically possible that some cases may be found in which the capillary flow cannot be entirely stopped regardless of the pressure in the armlet applied in the usual way. Lewis[3] has shown that blood flow in the forearm is not entirely stopped by the ordinary cuff because of some anastomoses which pass through the bone itself. In some of his work he was forced to use a cuff extending from shoulder to elbow. This difficulty has not been met by us clinically. However, since realizing this possibility we have learned that the effect of Lewis' broad armlet can be obtained with the ordinary cuff if it is placed so that its lower portion includes the upper portion of the elbow joint. We have taken this precaution in our later cases, though for all practical purposes it seems not to have made the slightest difference.

It is possible that localized arteriolar constrictions might lead to localized capillary flow in the absence of flow in the larger vessels. To the best of our knowledge we have not seen this clinically, though to and fro movements are common. We believe that this factor can be eliminated if repeated observations made on different capillaries be found to be in close agreement.

One would expect that all readings would be a little low if the mercury were permitted to drop steadily, for there must be an appreciable period between the release of pressure in the brachial artery and initiation of flow in the capillaries. Our results would seem to support this, but the more slowly the pressure falls, the less the error.

Finally, it has been suggested that in cases of increased venous pressure the flow may not begin until the pressure is definitely below systolic.[1] We have no data concerning this, but have taken the precaution of raising the pressure quickly above systolic at the beginning; and, if there has been a preceding period of venous congestion, we have always allowed several minutes' rest before starting a determination.

It must be remembered that all factors causing fluctuations in blood pressure will be as operative in this method as in any other. Thus we found it absolutely necessary to allow a patient who has just come upstairs from a ward at least five or ten minutes' rest, with a blood pressure cuff in place, before starting actual determinations. In practice, this period can readily be utilized in the selection of suitable capillaries.

RESULTS

A considerable number of persons were observed in whom the blood pressure could be obtained in the usual manner, that is, by auscultation. The systolic blood pressure obtained by capillary observation was found to vary between five and twelve millimeters of mercury lower than that obtained immediately afterward by auscultation. As examples the first five cases studied are listed, though the others varied within the same range.

CASE	SYS. B.P. (AUSCULTATION)	SYS. B.P. (CAPILLARY METHOD)
1	138	130
2	108	98
3	112	105
4	112	110
5	168	162

The patient with absence of pulsation in both arms was then reexamined. In his case it would seem to be correct to speak of mean pressure rather than systolic pressure in the brachials. It is to be recalled that blood pressure in the legs was 182/80 at the time of the determination. Readings by capillary method were unusually clear and easy to obtain. Mean pressure was found to be 38 mm. of mercury in the right arm and 35 mm. in the left.

This unusually low reading was not anticipated, though it was recognized that if such figures could be taken as applying to the cerebral circulation they might readily account for the peculiar attacks of syncope and convulsions. Therefore, one of us (L. H. C., Jr.) attempted to measure the intra-arterial pressure in the upper extremity by a direct procedure. Though the brachial artery could not be palpated, the skin and subcutaneous tissue overlying the normal anatomical site of the artery were infiltrated with 1 per cent novocaine. A No. 12 gauge steel needle connected to a 10 c.c. Luer syringe with a threeway stopcock intervening between the two was used. The side arm of the threeway stopcock was connected by a piece of short rubber tubing to glass manometer tubing 1.5 mm. in diameter.

The left brachial artery was found to be in normal position and was entered without difficulty. After about 3 c.c. of blood had entered the syringe, the stopcock was turned and the blood allowed to flow into the vertical manometer tubing. On repeated observations the maximum height to which the blood column rose was 410 mm. No pulsation was observed in the level of the blood in the manometer. If correction is made for the specific gravity of blood and of mercury, this gives a direct intra-arterial pressure of 32.2 mm. of mercury. This compares fairly well with the reading of 35 mm. obtained by the indirect capillary method.

SUMMARY

A method is described for obtaining blood pressure in the brachial artery by brachial compression with a blood pressure cuff and simultaneous ob-

servation of blood flow in the digital capillaries of the nail bed. This method consists in occluding the brachial artery with a pressure above systolic, waiting for cessation of flow in the digital capillaries, then slowly lowering pressure until flow is just resumed. This point is taken as systolic pressure or, in a case without pulsation, as mean pressure. As the method does not require pulsation, it is especially valuable in those cases in which pulsation is absent. Results obtained are compared with those obtained by auscultation in normal persons. One patient without pulsation in the brachial arteries was studied, and the results were confirmed by a direct pressure reading after arterial puncture.

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STUDIES OF THE ELECTRICAL FIELD OF THE HEART. I. INVARIANTS OF THE ELECTROCARDIOGRAM*†

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IT WAS the variability in the appearance of the electrocardiographic deflections that led Einthoven to advocate the use of the standard three leads. He believed that these leads would give a better idea of the potential set up by the heart than would one lead alone. This variability in appearance has also been shown to exist among leads other than the standard three usually employed (Cohn,[1] Wilson[2]). In addition, it has been shown that the appearance, especially the amplitude, of the deflections is dependent upon the electrical resistance of the tissues between the heart and the electrodes and on the electrical shunting of the body fluids. Both of these are quantities which vary with the leads employed as well as with other conditions (Zeisler,[3] Katz[4]). Every electrocardiogram is dependent on (1) the electrical changes in the heart muscle, (2) extracardiac factors independent of the particular lead employed (e. g., pericardial effusion, emphysema, etc.), and (3) extracardiac factors depending on the particular lead employed.

It was the purpose of this research to see whether or not the durations of the various intervals and deflections, the algebraic sum of the deflections in the QRST interval, and Einthoven's quantity were independent of the lead employed. Any quality of the electrocardiogram which is independent of the lead employed we have designated as an *invariant*.[5] Einthoven's quantity is defined as follows: If from two electrodes A and B the wires are so connected to the galvanometer that a current passing through the galvanometer from B to A gives an upward deflection, then the lead is called AB, or the lead from A to B; if the wires are reversed, the lead is BA. Let any three points A, B, C be connected so as to give the leads AB, BC, AC, called I, II, III respectively. Let the deflections at simultaneous points of the electrocardiograms of these leads be e_1, e_2, e_3 respectively. The quantity we wish to consider is $\Delta = e_2 - e_1 - e_3$. For the three standard leads Einthoven's law is $\Delta = 0$. It has been stated that Einthoven's law $\Delta = 0$ is exactly satisfied for *every* three leads AB, BC, CA (Wilson et al.[6]). Furthermore, Wilson et al.[7] have attached significance to the algebraic sum of the deflections in the QRST interval.

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PROCEDURE

Electrocardiograms with a large number of leads (about 150) were taken on a single individual. The electrodes consisted of circular sheets of German silver about 4 cm. in diameter, each with a binding post, shielded from moisture, to accommodate two wires. The electrodes were placed on various parts of the skin with a paste of flour and concentrated saline. Electrocardiograms were recorded on one film from two leads simultaneously. The location of simultaneous points on the two leads was determined by measuring the phase difference between the two curves of the same lead recorded simultaneously by both instruments. This was, of course, essential in calculating the Einthoven expression.

RESULTS

In every lead in our subject (as shown in Figs. 1, 2 and 3) the record consisted of a sequence of cycles of deflections (or waves) corresponding to the cycle of the heart beat. The sequence, though not regular, was the same in all leads. Each cycle was composed of two sets of deflections, the auricular and ventricular, the latter made up of an initial and final complex, often separated by an approximately isoelectric line. This division into P, QRS and T is independent of the particular lead used; the fact that in some leads the P or the T complex is not seen does not alter this division, for such a curve may be considered a special case in which the P or the T complex is isoelectric. Hence the sequence of cycles of deflections, the rhythm of the sequence and the division of each cycle into three groups of deflections, the P, QRS and T, are invariants.

The intervals of the cycle were not all easily measured because the beginning of T and sometimes the beginning of P were not sharply demarcated. It was found most convenient to measure (1) the duration of P, (2) the time interval between the beginning of P and the beginning of QRS, the so-called P-R interval, more properly called the P-Q interval, (3) the duration of QRS, (4) the time interval between the beginning of QRS and the beginning of T, the Q-T interval,* (5) the time interval between the beginning of QRS and the end of T, the QRST interval.

In the various different leads taken by us on any one day the maximum and the minimum P-Q intervals never differed by more than 0.03 sec., and in two simultaneous leads never by more than 0.02 sec. With many additional leads it was found that this range is not increased, so that P-Q is an invariant within 0.03 sec.

In some leads the P complex is so small that it is seen with difficulty, but where it can be seen its duration does not vary from lead to lead by more than about 0.01 sec. The beginning of QRS is always seen and the end of QRS usually; the duration of QRS does not vary by more than about 0.01 sec.

*Q-T has been given other meanings but in this report will be used in only the sense here defined.

It may be impossible to measure accurately the S-T interval because the beginning of T cannot always be seen. This is due to the fact that S-T is

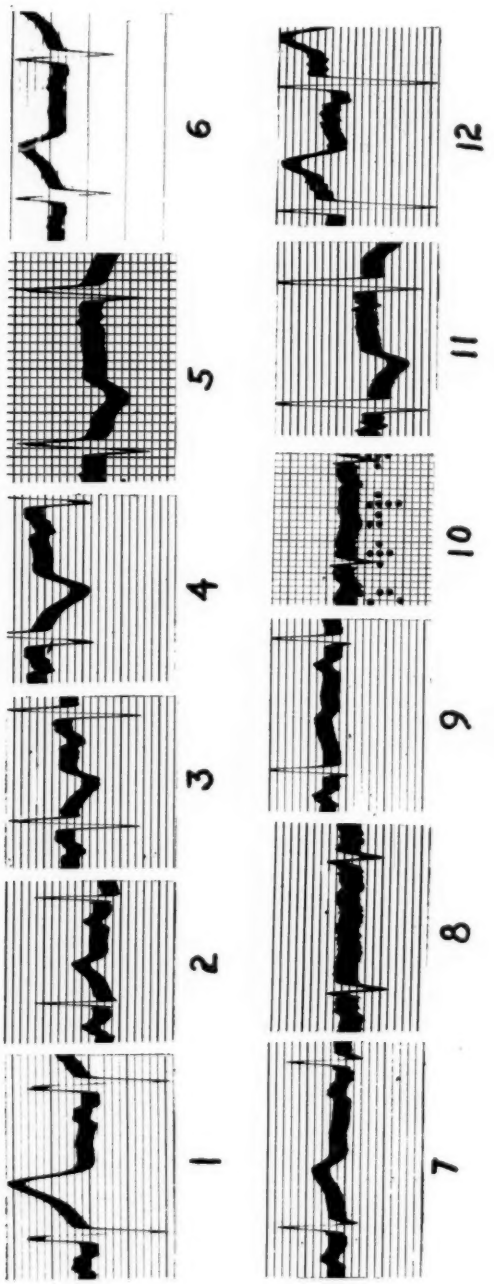

Fig. 1.—The curves, from the same person with different leads, are selected to show the following: leads 1 to 7, variability in P; leads 2, 8, 9, 10, 11, 12 the variability in QRS; lead 11, deep Q; leads 13, 14, 15 notching and splintering of QRS; leads 1, 4, 7, 9, 13, 16, 17 variability in T; leads 1, 11, 12 variability in S-T.

very often not isoelectric and often not horizontal. In Fig. 1, Lead I, for example, it is not possible to see just where on the rising limb of the S-T

segment T begins. When the beginning of T is clearly seen, it is found that the Q-T interval is very nearly invariant, just as is the P-Q interval; if this interval is measured from the beginning of QRS in those leads in which the beginning of T is not seen, a point is found on the curve which appears as though it may very well be the beginning of T. Hence for

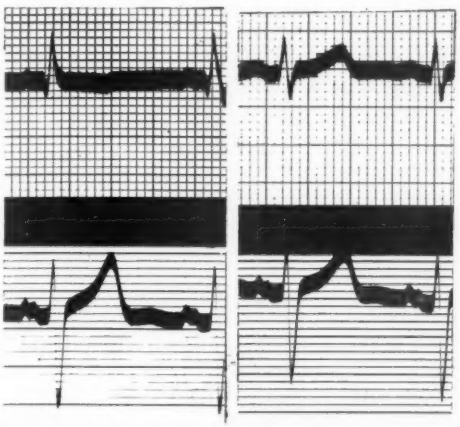

Fig. 2.—The leads of the figure form an Einthoven triangle. The Einthoven expression was calculated for this triangle by using simultaneous points of the curves of the two leads. (Note the difference in appearance of the common lead in the two segments of the figure—top lead in each. The explanation for this will be discussed in a subsequent paper.)

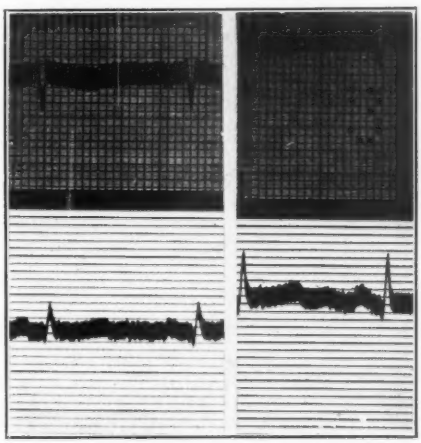

Fig. 3.—The leads of this figure form another Einthoven triangle. The Einthoven expression was calculated for this triangle also. (Note, for contrast, with Fig. 2, the similarity in appearance of the common lead in the two segments of the figure—top lead in each.)

practical purposes Q-T is an invariant and therefore S-T is also an invariant. Similarly, it is found that QRST is an invariant within about 0.02 sec.

Consequently, all the time relations of the electrocardiogram are invariants, namely, the duration of P, of QRS, of QRST, the P-Q interval, the S-T interval, and therefore also the duration of T.

In Fig. 1 are shown selected leads illustrating the wide variation in direction, number of phases, amplitude, contour, slope, slurring, notching and splintering of the P-wave (leads 1 to 7), QRS complex (leads 2 and 8 to 12) and T-waves (leads 1, 4, 7, 9, 13, 16 and 17). Attention is drawn to the deep Q-wave in lead 2 in this normal individual, which indicates that this wave, to which some significance has been attached, is not an invariant. In leads 13, 14 and 15 there is notching and splintering of QRS, not near the base line, and in lead 15 this occurs in a relatively large deflection. This has been considered significant by Pardee,[8] but as this study shows, slurring and notching of QRS are not invariants. It is apparent that the slope of a deflection is completely determined by its amplitude and its duration, and slurring is determined by the slope alone; for example, in lead 8 the deflections of QRS are slurred because their slope is smaller than in lead 12 where they are not slurred.

The segments between waves also vary in these leads. In lead 3 the curve between P and Q is above the isoelectric line, in lead 1 below. In leads 1, 11 and 12 are seen elevation and depression of S-T and variation in its slope.

An inspection of Fig. 1 will show that the algebraic sum of the areas between the deflections of the QRST interval and the base line of one cycle is obviously not an invariant[7]; in lead 2 it is small and positive, in lead 17, large and negative.

A similar analysis of the Einthoven quantity, which Wilson[6] recently asserted, on theoretical grounds, to be equal to zero for any three points of the body, showed that it is not an invariant. For example, in Fig. 2 we found a pair of simultaneous points where $\Delta = -15.3$, in Fig. 3 a pair where $-2 < \Delta < 0$. In many other sets of leads Δ was found to vary between 0 and –15. Consequently, it is *not* an invariant. (The explanation of this result in the face of theoretical arguments to the contrary,[6] will be considered in a subsequent paper.)

DISCUSSION

This analysis of multiple leads shows that the only known invariants of the electrocardiogram are the time relations of the various deflections and the intervals between them. It is to be distinctly understood that we do not imply that the invariants are important and the noninvariants unimportant. In this paper we are simply differentiating those qualities of the electrocardiograms which are independent of the lead employed from those which vary with the lead. Too often significance is attached to changes in configuration in standard leads which might be due to alteration in the heart's position (cf. Katz and Ackerman[9]). The theoretical explanation of the observed results, and the significance of the invariants and of the noninvariants will be discussed in a subsequent paper.

SUMMARY

1. Every electrocardiogram depends on the electrical changes in the heart muscle and on extracardiac factors, some of which are independent of, and others dependent on, the particular lead employed.

2. By using many different leads (about 150) on one individual the invariance of various properties of the electrocardiogram was investigated to determine which properties were invariants, i. e., independent of the particular lead used.

3. The only known independent invariants of the electrocardiogram are its time relations, namely, the sequence of cycles, their rhythm, the division of each cycle into three complexes, the duration of P, of QRS, of QRST, of T, and of the P-R (P-Q) and S-T intervals.

4. All other properties studied, such as direction, amplitude, contour, notching, slurring, the algebraic sum of the initial and final ventricular deflections, and the Einthoven quantity were found to be noninvariants.

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ELECTROCARDIOGRAPHIC FINDINGS IN TUMORS OF THE HEART

With a Report of a Case*

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THE literature contains many reports of cases of cardiac tumors. Most of these reports are concerned with clinical and pathological findings and with discussions of the frequency and location as well as the character of the cardiac neoplasms. There is also a considerable number of reports of cardiac tumors in which electrocardiograms were obtained, but in only three of these are records presented.

These electrocardiograms do not show any uniformity of findings but, as might be anticipated, vary according to the chamber of the heart in which the tumors were located.

These deviations from normal are shown graphically in Table I.

The records obtained in the present case show remarkable resemblances to those obtained in cases of recent coronary thrombosis, but also have definite characteristic features which serve to distinguish them from those reported in such cases. Contrary to expectation there were no disturbances of the coronary arteries either by tumor cells or by arteriosclerosis or thrombi.

The purpose of this paper is to present the clinical and pathological findings in a case of metastatic tumors of the myocardium and to present the fourth series of electrocardiograms reported in patients with cardiac tumors.

Both primary and secondary tumors of the heart have been reported by many authors and for the most part were diagnosed only at postmortem examination. In a series of 37,777 autopsies reported by Morris,[4] Willius and Amberg,[8] and Peters and Milne,[14] 159 cases or approximately 0.4 per cent showed secondary tumors of the heart. At this hospital three cases of metastatic tumors of the heart have been found in 592 autopsies, which is approximately 0.5 per cent. These three cases, including the one in this report, are all those of lymphosarcoma, the first two showing nodules in the wall of the left auricle without clinical evidence of cardiac involvement. Of these 592 autopsies 44 (approximately 7.4 per cent) were in cases of malignant disease.

Metastases to the heart have occurred from all the principal organs of the body in which malignant tumors are commonly found, and have reached the heart by three routes: (a) by lymphatic vessels, (b) by

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invasions of veins and tumor cell embolisms through blood vessels, (c) by direct extension from a tumor in the vicinity of the heart. (Kauffman.[12]) Morris believes that tumors are carried to the heart by the blood stream in most instances. In the case here reported metastases occurred apparently by lymphatic or blood vascular route, although no tumor thrombi could be demonstrated in the vessels.

Most observers (Kauffman,[12] Napp[13]) state that the right side of the heart is more often involved than the left. In our case the muscular wall of the left ventricle and interventricular septum are extensively involved.

TABLE I

AUTHOR	LOCATION OF TUMOR	RHYTHM	AXIS	P-R INTERVAL	QRS INTERVAL	QRS COMPLEX	T-WAVE	S-T SEGMENT
Lloyd[7]	A-V Node	Normal sinus	Normal	.17-.28 sec. Dropped beats	Normal	Normal	Upright	Isoelectric
Willius & Amberg[8]		Normal sinus	Right deviation	.12 sec.	Prolonged .12 sec.	Notched	Inverted in II & III. Upright in I	Elevated in I and II, depressed in III, convex
Houck & Bennett[9]	Left auricle	Normal sinus tachycardia	Normal	.16 sec.	Normal .08 sec.	Low voltage	Slightly diphasic I & II (digitalis?)	Concave (digitalis?)
Siegel & Young	Left ventricle and septum	Sinus tachycardia	Normal	.16 sec.	Normal .04-.06 sec.	Normal	Inverted all leads	Convex slightly depressed II and III

Statements as to the relative frequency of sarcoma and carcinoma found in the heart are conflicting. Authors (Morris, Willius and Amberg) who believe that secondary carcinomas are more frequent may not really be in serious disagreement with others (Kauffman) who believe that sarcomas are more frequent since, as Goldstein[2] states, "There are probably many cases of secondary sarcoma of the heart that are never reported in the literature. They are comparatively not much less common than secondary cancer of the heart."

The clinical picture of tumor of the heart is variable, and there are no pathognomonic signs (Morris). At the time he wrote (1927) the condition had never been diagnosed intra vitam. The case of reticulum cell sarcoma with metastases involving the wall of the ventricle here reported is of interest in that the tumor of the heart was suspected antemortem because of certain electrocardiographic findings.

Armstrong and Mönckeberg[1] in 1911 reported a case with a Jacquet polygraphic tracing which showed complete auriculoventricular heart-block. This tumor was primary in the heart.

Darier[3] in 1927 published a report of a cardiac tumor which he found in a case of mycosis fungoides. Tumors causing a clinical syndrome resembling subacute bacterial endocarditis have been reported by Carnot and Lambling in 1928.[5]

Lloyd[7] published in 1929 the first electrocardiogram in a proved case of tumor of the heart. His tracings showed sino-auricular rhythm with a P-R interval up to 0.28 seconds, thus constituting first degree A-V block. The tumor was found in the region of the A-V node and was probably an endothelioma.

Willius and Amberg[8] in 1930 reported two cases of metastatic tumor of the heart, one of which was diagnosed ante mortem. Their electrocardiograms of one case, a child of eight years, showed incomplete bundle-branch block, with negative T-waves in Leads II and III and a slight elevation of the S-T segments in Leads I and II with a depression of the S-T in Lead III. There was also a moderate degree of right axis deviation. Clinically the patient showed signs of myocardial failure. Postmortem examination showed a metastasis from an endothelioma of the left femur. A second electrocardiogram taken one month after the first was essentially unchanged. Their second case was one of leucosarcoma of the heart in a child of two and a half years. No electrocardiograms of this case were published.

Houck and Bennett[9] in 1930 reported a tumor of the left auricle (polypoid fibroma) in which the electrocardiogram showed sinus tachycardia with a rate of 120. The ventricular complexes were somewhat abnormal and the electromotive force was low. The T-waves in Leads I and II were slightly diphasic. However, their patient had received digitalis before admission to the hospital, so that these T-wave abnormalities may have been due to the drug.

Fishberg[10] in 1930 reported three interesting cases in which secondary malignant growths in the right auricle were accompanied by auricular fibrillation or flutter which led during life to the opinion that the known malignant tumor had invaded the right auricle. He did not publish any electrocardiograms.

Yater[11] in 1931 gave a comprehensive review of all the literature and reported nine cases of his own. He published no electrocardiograms.

CASE REPORT

Clinical Summary.—N. M., aged forty-seven years, Italian, gardener, was first seen January, 1931, presenting himself with a complaint of a "lump" in the left lower abdomen of two months' duration. This mass was painful and was increasing in size. There were no other significant symptoms. However, he had lost fourteen pounds in weight since the onset of the illness. On January 23, 1931, he was seen

in consultation with the surgical service because of feeble heart sounds. At this time he denied precordial or substernal pain either at rest or even with severe effort. He was also positive that he had never noticed any dyspnea either nocturnal or diurnal, either at rest or with effort. He had never had any symptoms suggesting collapse or any severe epigastric pain.

On examination the patient was found to be poorly nourished and somewhat pale. He was not dyspneic and there was no orthopnea or distention of the veins

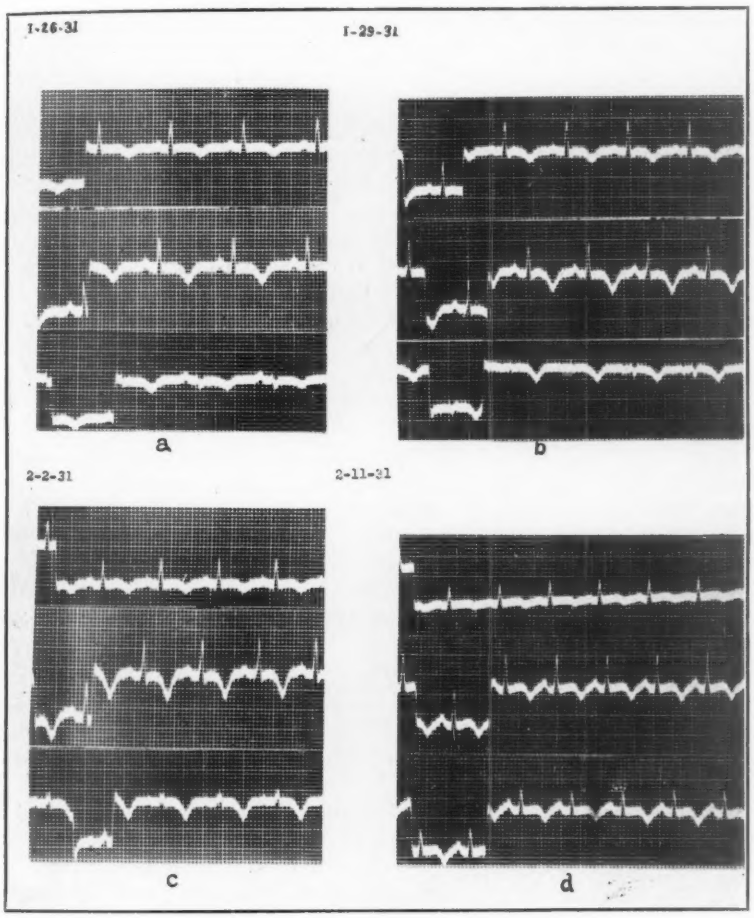

Fig. 1.—Electrocardiograms taken from January 24 to February 11, 1931. T-waves inverted in all leads in all records. R-T segments are convex in all records. The T-waves are "cove plane" in all leads. Duration of P-R and QRS intervals are all within normal limits. "Take-off" of T-waves is isoelectric in all records. Note the lack of significant change during this time.

of the neck. The lungs were free from abnormal signs, but the heart sounds were weak and distant. It was this finding which first drew attention to the heart and which prompted the request for the medical consultation and the electrocardiogram. The heart was not demonstrably enlarged and no murmurs were heard. The rate was 86 per minute and the pulse was rhythmic and regular. There was moderate peripheral arteriosclerosis with a blood pressure of 92 mm. systolic and 68 mm. diastolic. The liver was palpable but the spleen and kidneys were not. In the left

upper quadrant of the abdomen there was a hard nodular mass which seemed to be about ten centimeters in diameter. This was not movable. There was no enlargement of the palpable lymph nodes. Neurological examination was negative. The tentative diagnosis was malignant disease of the colon.

Laboratory Findings.—On admission the urine contained a faint trace of albumin, and tests for urobilin and urobilinogen were strongly positive. No blood was present in the urine either grossly or microscopically. Slide precipitation tests for syphilis and Wassermann reaction were negative. Red blood cells numbered 3.2 million per c. mm. Hemoglobin was estimated at 65 per cent (Tallqvist). White blood cells numbered 19,000 per c. mm. Differential count of leucocytes showed polymorphonuclear neutrophiles 88 per cent; lymphocytes 11 per cent; others 1 per cent. There was slight anisocytosis.

Roentgenoscopic studies of the gastrointestinal tract revealed no abnormal findings. A roentgenogram of the heart several days after admission showed moderate bulkiness of the left ventricle and some infiltration in the base of the right lung.

Electrocardiographic tracings recorded on four occasions are shown in Fig. 1. Fig. 1*a* is the record taken January 26, 1931. It shows normal sinus rhythm, normal QRS complexes in all leads and inverted T-waves in all leads. The S-T portion is isoelectric in all leads. The T-waves in Leads II and III have somewhat rounded shoulders. The duration of the P-R and QRS intervals is well within normal limits. (0.16 seconds and 0.04 seconds respectively.) Fig. 1*b* is a record taken three days later and resembles the first one except for a somewhat deeper inversion of the T-waves in Leads II and III and a somewhat greater rounding of the shoulders of the T-waves in all leads. Fig. 1*c* is a record taken four days later. This record shows still deeper inversion of the T-waves in Leads II and III and a somewhat shallower T-wave in Lead I. The convexity of the S-T segment is greater than in the two preceding records, especially in Leads II and III. The "take-off" of the T-waves is very slightly (1 mm.) below the isoelectric level.

Fig. 1*d* is an electrocardiogram recorded nine days after the one in *c* and shows the T-waves to be somewhat less deeply inverted than those of *b* and *c*. The "take-off" of the T-waves in Leads I, II and III is now slightly above the isoelectric level. The rounding of the shoulders of the T-waves in Leads II and III is slightly greater than that in the previous records.

The patient's course in the hospital progressed unfavorably. He developed pneumonia at the right base with sharp rise in temperature which was probably the cause of the infiltration observed in the roentgenogram. Recovery from this infection occurred. On February 11, he bled severely from the rectum, going into shock. Apparently the tumor had eroded into the lumen of the bowel. His blood count during the hospital stay fell to 2.6 million red blood cells per c. mm. and later to 1.2 million. The patient died on February 12, following the hemorrhage. A few hours before death a pericardial friction rub was heard over the entire precordium.

Autopsy Findings of Interest.—The case was one of reticulum cell or large round cell lymphosarcoma apparently arising in a mesenteric lymph node, with extension into the wall of the duodenum, and metastasis throughout the viscera including the wall of the left ventricle which was extensively involved.

The heart weighed 315 grams. There was a large tumor mass approximately 5 cm. in diameter involving about one-half of the wall of the ventricle and about one-third of the interventricular septum. On the external surface of the heart the tumor formed a slightly bulging mass grayish white in color extending toward the apex, the distribution of the tumor resembling that of an infarct due to occlusion of the descending branch of the left coronary artery. No tumor cell thrombosis of the large or small branches of the coronary artery was demonstrable, either grossly or microscopically. Tumor cells had, however, invaded the walls of the thin-

walled veins and in places projected irregularly into the lumen. The coronary arteries were thin-walled and free from arteriosclerotic changes and thrombi. The epicardium as well as the myocardium was invaded by tumor on the posterior surface of the heart. There were small tags of fibrous tissue invaded by tumor cells which were the only anatomical alteration which might have caused the pericardial friction rub heard clinically. In addition to the large tumor mass mentioned above, there was a small tumor nodule approximately 6 mm. in diameter just beneath the

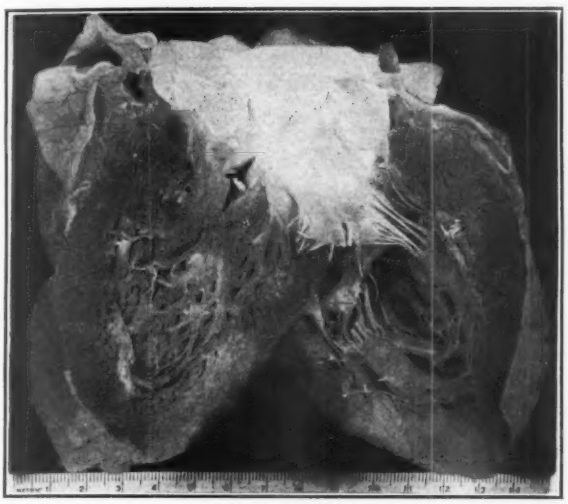

Fig. 2.

Fig. 3.

Figs. 2 and 3.—Metastatic reticulum cell sarcoma of the myocardium. Gross characteristics.

endocardium in the region of the undefended space. Sections through this nodule showed the tumor involving the myocardium only and not extending to the region of the conduction fibers or overlying endocardium.

The gross appearance of the tumor is seen in Figs. 2 and 3. Grossly, the tumor was of fine architecture and on careful inspection of the periphery of the tumor the myocardial fibers were still recognizable. This was borne out by its microscopic

appearance in which the cells were seen to infiltrate and separate the normal structures rather than destroy them, in this respect resembling the leucemic infiltrations rather than destructive tumors.

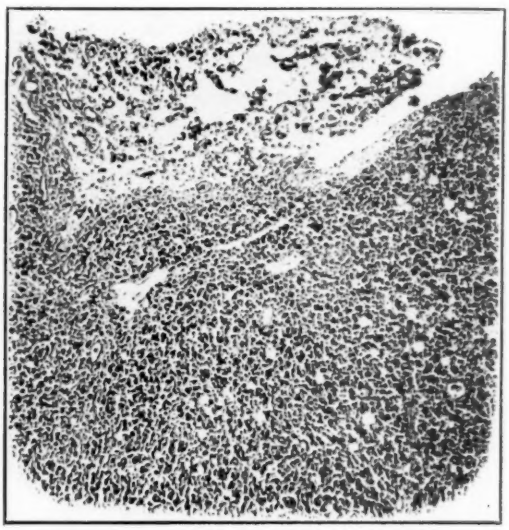

Fig. 4.—Photomicrograph, low-power magnification, metastatic reticulum cell sarcoma of the myocardium, extending through the epicardium.

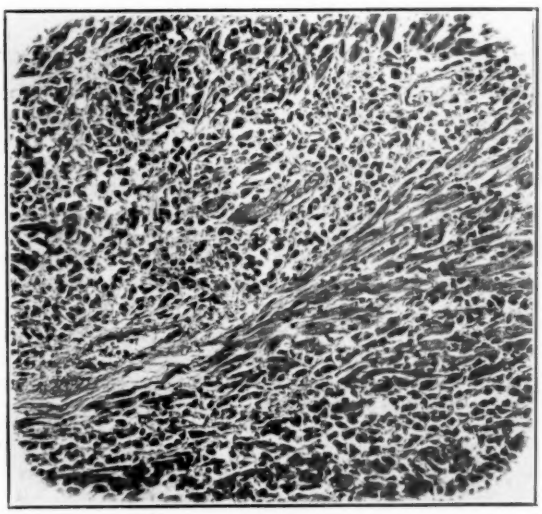

Fig. 5.—Photomicrograph, metastatic reticulum cell sarcoma of the myocardium, showing the tumor cells infiltrating the muscle fibers.

The largest tumor mass in the body was in the mesenteric fan extending into the wall of the duodenum with ulceration of the wall. The distribution suggested that the tumor arose in the mesenteric lymph nodes or possibly in the lymphoid tissue of the duodenum. In addition to the metastases in the heart there were secondary tumors in the kidneys, spleen, mesenteric lymph nodes, serosa of the sig-

moid colon, right adrenal, and gall bladder. There were no metastases present in the lungs or in the liver.

The microscopic characteristics of this tumor in the heart are shown in Fig. 4. Round cells, varying considerably in size, predominate. The nuclei of these were large, hyperchromatic, and in many cases in mitosis. Some of the cells were polygonal, many of the nuclei were indented and many were multinucleated. The cells resembled those of germ centers of lymph follicles. Oxidase stains on frozen sections of the tumor showed no oxidase granules present. The tumor stroma was scanty.

DISCUSSION

When the electrocardiograms in our case were first studied, it was thought that the changes were produced by myocardial damage from coronary artery disease. In repeated questioning of the patient all symptoms of cardiac embarrassment, such as precordial, substernal or epigastric pain or dyspnea, either at rest or with effort, were denied. There were no physical signs of cardiac failure. X-ray examination of the heart did not reveal any significant abnormalities. In addition to all these observations, closer study of the tracings revealed that the T-waves were constantly inverted in all leads in every record, and their direction was not reciprocal in Leads I and III as is usually the case in recent coronary thrombosis. Moreover, there was no significant change from day to day as one would expect in recent coronary occlusion. The S-T segments of all the tracings were isoelectric or practically so. Accordingly, it was suspected that a metastasis in the heart was quite possible. This concordance in the direction of the T-waves in all leads associated with "cove-plane" T-waves and convex S-T segments without significant deviation of these S-T segments from the isoelectric level may well be dependent upon the changes induced in the electrical effects of the myocardium by the presence of the tumor.

From the records one would assume that the main divisions of the conduction system were preserved intact and such proved to be the case. These changes in T-wave direction were not produced by abnormally high skin resistance, for in such cases QRS waves and T-waves are altered in the same direction. Katz[6] states that inverted T-waves are to be regarded as the result of a disturbance in the pathway of retreat which simulates persistence of activity in the region of the apex of the left ventricle. In other words there may be a delayed offset of activity or a relative prolongation of activity or both. Attention is called to the fact that this tumor occupied that portion of the left ventricle ordinarily supplied by the descending ramus of the left coronary artery. It should be remembered that the coronary arteries and their branches in this area were not obstructed by tumor cells, thrombi, or arteriosclerotic plaques.

SUMMARY

1. The case reports of tumor of the heart have been reviewed. Where electrocardiograms have been recorded, they have been analyzed and

compared with those recorded in our own case. The frequency of cardiac tumors together with their location in the heart has been discussed.

2. A case of metastatic cardiac tumor with electrocardiograms is reported.

3. The similarity of the electrocardiographic findings in a case of tumor of the heart and in myocardial changes from other causes is pointed out, especially the similarity of records in cases of coronary disease.

4. The distinctions between records of coronary disease and those of tumor are noted, especially the lack of reciprocal direction of T-waves in Leads I and III and the failure to show deviation from the isoelectric level in the S-T segments.

5. The changes seen in electrocardiograms in tumor cases give some evidence as to the location of the neoplasm in the heart.

We wish to express our indebtedness to Dr. Harold Feil and Dr. B. S. Kline for their valuable assistance in the study of this case and in the preparation of this paper.

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THE ELECTROCARDIOGRAM IN DIABETIC COMA*

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CORONARY sclerosis is comparatively common among diabetics as a group.[1, 2, 3] Coronary occlusion is a recognized complication of diabetes, particularly in cases where the blood sugar has been rapidly brought down from a high to a low level by insulin treatment.[3, 4] The signs and symptoms of coronary occlusion may be masked by diabetic coma. Therefore, it appears to us of practical value in the recognition of coronary disease in diabetic coma, to find out what effect, if any, diabetic coma itself may impose on the electrocardiogram.

In diabetic coma there are a number of known deviations from normal conditions which must be considered separately in regard to their possible effects on the electrocardiogram. The most evident of these are acidosis, hyperglycemia, uremia and low blood pressure.

Acidosis and Hyperglycemia.—It has been shown in experimental animals that slight changes in the P_H of the blood toward the acid side will cause a slowing of the sinus rhythm, delayed auriculoventricular conduction, marked changes in the ventricular complexes, lengthening of the refractory period of both auricular and ventricular muscle, and a tendency to the appearance of ventricular premature beats.[5, 6, 7] However, no published data have been found to indicate that the degree of acidosis reached in disease is sufficient to cause such disturbances. It is true that the frequency of heart disease in patients with diabetes has led to the belief among some clinicians that diabetes exerts a specific toxic effect upon the myocardium, and reference has been made to a "cardiac type" of diabetic coma.[8] Indeed, "the toxic products of the acetone bodies" have been incriminated as the agent causing failure in these cases and digitalization has been recommended.[9] However, these clinical impressions have not been supported by electrocardiographic or pathological evidence. In a careful study of 123 diabetic patients Hepburn and Graham found no relation between the electrocardiographic abnormalities and the existing level of blood sugar or degree of acidosis.[10]

Uremia.—It is generally recognized that uremia, like many other intoxications, may have a depressant effect on the T-waves. Some of the electrocardiograms of patients with uremia, published by Wood and White, show T-waves of the characteristic "coronary" type.[11] The high

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TABLE I

OBSERVATIONS ON PATIENTS DURING COMA

CASE NUMBER	SEX	AGE	CLINICAL CONDITION*	BLOOD SUGAR IN MG. PER 100 C.C.	BLOOD CO_2 COMBINING POWER IN VOLUMES PER CENT	BLOOD NONPROTEIN NITROGEN IN MG. PER 100 C.C.	RECTAL TEMPERATURE IN DEGREES FAHRENHEIT	BLOOD PRESSURE		ELECTROCARDIOGRAM DURING COMA								
								SYSTOLIC MM. HG	DIASTOLIC MM. HG	RHYTHM	RATE PER MIN.	P-R INTERVAL IN SECONDS	QRS INTERVAL IN SECONDS	T-WAVE IN LEAD I	T-WAVE IN LEAD II	T-WAVE IN LEAD III	ELECTRICAL AXIS	REMARKS ON ELECTROCARDIOGRAM
1	F	25	Mild coma	180	22	47	100.2	110	80	Sinus tachycardia	115	0.12–0.14	0.08	Up	Up	Up	Normal	High skin resistance
2	F	19	Coma	440	17	27	99.8	120	86	Sinus tachycardia	110	?	0.08	Up	Up	Up	Normal	P-waves not clear
3	M	13	Coma	380	20	38	95	100	70	Sinus tachycardia	145	0.16	0.08	Up	Up	Up	Normal	High skin resistance
4	F	37	Deep coma	420	10	67	97	100	60	Sinus tachycardia	115	0.16	0.08	Up	Diphasic	Diphasic	Normal	High skin resistance
5	M	49	Coma	480	15	77	98	140	?	Sinus tachycardia	140	0.16	0.08	Up	Up	Inverted	Left	High skin resistance
6	F	46	Very drowsy	620	3	71	101.6	98	80	Sinus tachycardia	140	0.12	0.08	Up	Up	Diphasic	Normal	One ventricular extrasystole. High skin resistance
7	F	23	Deep coma	500	8	48	101	100	70	Sinus tachycardia	140	0.12	0.10	Up	Up	Inverted	Normal	High skin resistance
8	M	13	Coma	880	17	Not recorded	99.8	60	?	Sinus tachycardia	160	0.12	0.06	Up	Up	Up	Normal	High skin resistance
9	F	27	Deep coma	370	3	23	96	138	82	Sinus tachycardia	130	0.18–0.20	0.06	Up	Low	Diphasic	Normal	Slightly low origin T_1
10	M	35	Deep coma	360	4	39	95.6	130	80	Sinus tachycardia	109	0.14	?	?	?	?	Normal	Deformed by high resistance
11	F	18	Coma	420	11	34	98.6	106	60	Sinus tachycardia	111	0.14	0.08	Diphasic	Diphasic	Diphasic	Normal	High skin resistance
12	F	38	Coma	270	8	35	97.2	120	80	Sinus tachycardia	107	0.16	0.08	Flat	Low	Flat	Normal	High skin resistance
13	M	13	Very deep coma	680	4	54	96.2	90	?	Sinus tachycardia	160	0.12	0.06	Up	Up	Inverted	Normal	High skin resistance
14	M	18	Coma	320	12	28	99	124	82	Sinus tachycardia	111	0.16	0.10	Up	Up	Inverted	Normal	High skin resistance
15	M	14	Deep coma	480	7	40	99.4	Not obtainable		Sinus tachycardia	130	0.14	0.08	Up	Diphasic	Inverted	Normal	High skin resistance

*In all cases examination of the heart was recorded as negative except in Case 15 in which it was noted that the heart sounds were "distant."

TABLE II

OBSERVATIONS ON PATIENTS AFTER EMERGENCE FROM COMA

CASE NUMBER	INTERVAL BETWEEN FIRST AND SECOND OBSERVATIONS IN DAYS	CLINICAL CONDITION*	BLOOD SUGAR IN MG. PER 100 C.C.	BLOOD CO_2 COMBINING POWER IN VOLUMES PER CENT	BLOOD NONPROTEIN NITROGEN IN MG. PER 100 C.C.	ORAL TEMPERATURE IN DEGREES FAHRENHEIT	ELECTROCARDIOGRAM AFTER COMA								
							RHYTHM	RATE	P-R INTERVAL IN SECONDS	QRS INTERVAL IN SECONDS	T-WAVE IN LEAD I	T-WAVE IN LEAD II	T-WAVE IN LEAD III	ELECTRICAL AXIS	REMARKS ON ELECTROCARDIOGRAM
1	7	Good	140	Not recorded	31	98.6	Normal rhythm	94	0.12	0.08	Up	Up	Up	Normal	High skin resistance
2	8	Good	80	Not recorded	Not recorded	98.4	Normal rhythm	90	0.16	0.08	Up	Up	Up	Normal	High skin resistance
3	3	Good	120	Not recorded	Not recorded	99.2	Normal rhythm	85	0.14	0.08	Up	Up	Up	Normal	High skin resistance
4	1	Good	330	10	66	101	Sinus tachycardia	130	0.16	0.08	Up	Diphasic	Inverted	Normal	High skin resistance
			80	29											
5	2	Good	90		72	98.6	Normal rhythm	94	0.16	0.08	Diphasic	Diphasic	Inverted	Left	
6	Died after two days of otitis media and streptococcus meningitis. Autopsy.														
7	3	Good	70	32	39	100	Normal rhythm	92	0.16	0.09	Inverted	Diphasic	Diphasic	Normal	High skin resistance
			180	29											
8	2	Good	320	43	Not recorded	99	Normal rhythm	86	0.14–0.16	0.08	Up	Up	Up	Normal	
9	Died after two days of sepsis. No autopsy.														
10	Died on day of admission, of coma. No autopsy.														
11	No follow-up record obtained.														
12	2	Good	80	Not recorded	Not recorded	98.4	Normal rhythm	88	0.16	0.08	Up	Up	Flat	Normal	
13	2	Good	80	21	Not recorded	98.6	Normal rhythm	94	0.16	0.06	Up	Up	Flat	Normal	Slightly high skin resistance
			380	12											
14	2	Good	280	21	28	99	Sinus tachycardia	109	0.16	0.08	Flat	Low	Flat	Left	
15	2	Good	60	22	Not recorded	99	Normal rhythm	86	0.16	0.06	Up	Up	Flat	Normal	

*In all cases examination of the heart was recorded as negative except in Case 15 in which it was noted that the heart sounds were "distant."

level of nonprotein nitrogen in the blood of some cases of diabetic coma might therefore exert an effect of its own on the electrocardiogram.

Low Blood Pressure.—The blood pressure is often, though not constantly, lowered in diabetic coma, occasionally to such a degree that it is unobtainable by the usual auscultatory method.[12] This with other evidences of stagnation in the peripheral capillary bed might lead one to question whether there might not be similar changes in the myocardial circulation which would have an effect on the electrocardiogram.

PROCEDURE

Electrocardiograms have been taken immediately on admission in fifteen cases of diabetic coma at the New England Deaconess Hospital. Control electrocardiograms after emergence from coma were taken in eleven of these cases, from one to eight days later. Of the remaining four cases, three patients died and one left the hospital before a control record was taken. The clinical and laboratory data are summarized in Tables I and II. All of the cases were uncomplicated except Cases 5, 6 and 9 in which there were respectively hemochromatosis, streptococcus septicemia and sepsis. The patients varied in age from thirteen to forty-nine years, but only two were over forty years. There were eight females and seven males.

Clinically, the cases varied in severity from marked drowsiness to the most profound coma. The degree of acidosis as measured by the CO_2 combining power of the blood was ten volumes per cent or below, in seven of the thirteen cases in which it was recorded. The blood sugar levels ranged from 0.18 to 0.88 grams per 100 cubic centimeters. The nonprotein nitrogen of the blood was elevated above 35 milligrams per 100 cubic centimeters in nine of the fourteen cases in which it was recorded, the highest being 77. Fever was present in two cases (100° F. and 101° F. rectal respectively) and the body temperature was subnormal in five cases (95° F. to 97.2° F. rectal). The systolic blood pressure measured 100 milligrams Hg or below in seven cases. There were no cases of hypertension. Physical examination of the heart was negative in all cases except one in which it was noted that the heart sounds were distant.

ELECTROCARDIOGRAMS

All of the records were taken by means of a string galvanometer type of electrocardiograph, some being taken with a Hindle and the remainder with a Sanborn apparatus. An obstacle to precise analysis of the records taken during coma was presented by the high skin resistance which was uniformly present in these cases. The increased resistance was attributed to the low skin temperatures and the dryness of the skin. Efforts to overcome this by brisk scrubbing of the skin and application of hot water bottles were not successful. The resistance was still high in six of eleven cases in which the electrocardiogram was repeated after the coma had

cleared. In only one case, however, was the resistance high enough to interfere seriously with the interpretation of the ventricular complexes. The effect of high resistance in the circuit is to cause overshooting, with consequent exaggeration of the amplitude of individual complexes and sometimes to change a monophasic into a diphasic wave or to cause the T-wave to "take off" above or below the base line. In the presence of high resistance, therefore, one must be extremely cautious in interpreting abnormalities in the electrocardiogram. On the other hand, if the record is normal in spite of high resistance, one has only to discount a slight exaggeration in the amplitude of the deflections.

Of the fifteen records taken during coma all showed a sinus tachycardia; nine were otherwise completely normal. In two records the only abnormality was a diphasic T-wave in Lead II, and in one the T-waves were diphasic in both Leads I and II. In one case (Case 9) the T-wave in Lead II was of low amplitude, and there was slightly low origin of the T-wave in Lead I. In another (Case 12) the T-wave was flat in Lead I and low in Lead II. The decreased amplitude of the T-waves in these last two cases cannot be explained on the basis of high skin resistance. In Case 9 the patient died without regaining consciousness so that a control record was not obtained, but in Case 12 the control record showed normal T-waves. In three cases (Cases 5, 7 and 13) the opposite effect was observed, upright T-waves during coma, changing to flat, inverted or diphasic waves in the control record. No explanation is offered for this. It is of some interest that in Case 5 the patient died two months later from coronary thrombosis.

SUMMARY AND CONCLUSION

Electrocardiographic records have been taken in fifteen cases of diabetic coma. High skin resistance, which was uniformly present, offered a serious obstacle to precise analysis of the individual complexes. In nine cases the electrocardiogram was within normal limits, while in four others the abnormal feature (diphasic T_1 or T_2 or both) might be explained by "overshooting" due to the high skin resistance. In two cases the abnormalities could not be explained entirely on this basis. One showed a slightly low origin of the T-wave in Lead I with a low amplitude of T_2. The other showed a flat T_1 and low amplitude of T_2. Control electrocardiograms were obtained in eleven cases after emergence from coma. Of the four cases showing diphasic T-waves during coma, control records were obtained on two. One of these, in which high skin resistance persisted, still showed a diphasic T-wave in Lead II. The other, with normal skin resistance, gave a normal record. Of the two cases showing definite intrinsic electrocardiographic changes during coma, one patient died and the other gave a normal control record. Three cases with normal records during coma showed diphasic, flat or inverted T-waves in the control record.

The conclusion to be drawn from these cases is that electrocardiographic changes are not the rule in diabetic coma, and when present they consist

of minor T-wave abnormalities which are not likely to be confused with or to mask the picture of coronary occlusion.

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TRICUSPID STENOSIS

Review of the Literature and Report of a Case With Antemortem Diagnosis*†

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ACQUIRED chronic fibroplastic tricuspid stenosis is sufficiently rare to warrant reporting a case, especially if the diagnosis was made during life and confirmed at autopsy. While far from unknown this condition is rare enough to be neglected in many textbooks. Aschoff[1] and Henke and Lubarsch[2] make no mention of it; while Kaufmann[3] is content with saying that organic changes of the tricuspid valve are "vanishingly rare." Wiggers[4] does not mention it at all, and Strümfell and Seyfarth[5] say it is so rare as to have no practical importance.

FREQUENCY

Leudet[6] reviewed the literature to 1888 and was able to collect 114 cases. J. B. Herrick[7] reported three cases in 1897, bringing the total at that date to 154. W. W. Herrick[8] reported one case in 1908, bringing the total to 187. Futcher[9] reported five cases in 1911, total 195. Cottin and Saloz[11] reported one case in 1920, Gigaard[12] one in 1923, Hiller[13] one in 1925, Dressler and Fischer[14, 15] thirty in 1929 and three more in 1930, the Massachusetts General Hospital[16] one in 1930. Cabot[17] records thirty-three cases out of four thousand necropsies done at the Massachusetts General Hospital between 1896 and 1919; how many of these occurred before 1911 and were therefore presumably included in Futcher's review I do not know, but it is probably a fair estimate that not more than twelve of the thirty-three cases fall in the last eight of the twenty-three years. White[18] stated in 1927 that Levine said he had recently seen three cases, but no other reference to these was found. Tschilikin[19] refers to some observations of his in the Russian literature,[20] which I have not seen.

A study of the world literature to date has revealed only 232 cases of acquired tricuspid stenosis; if we include three cases of Levine, twelve of the Massachusetts General Hospital, and several of Tschilikin the total is increased to 250. Considering the enormous number of autopsies performed throughout the world this is a very low incidence, even lower than that indicated by its occurrence only seven times in 24,000 cases at the Johns Hopkins Hospital.[21]

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FREQUENCY OF DIAGNOSIS

The diagnosis of acquired tricuspid stenosis is usually not correctly made during life. Vacquez[22] says it is "difficult of diagnosis"; Norris and Landis[23] say the diagnosis "cannot be made with any certainty"; Mackenzie[24] says that in the majority of cases it is not recognized during life. In Leudet's[6] series of 114 cases the diagnosis had been correctly made intra vitam in only six. In the first 187 cases[8] it was made in ten, in the first 195 it was made in thirteen. In Henschen's[10] fourteen cases it was not made at all. Cabot[17] says, "Looking back over the whole thirty-three cases of this complicated group one sees that, *though the tricuspid valve was involved in every one* of them *we only suspected this disease in one out of the thirty-three and did not even consider it in the others.* . . . Tricuspid lesions we practically *do not recognize at all.*" Dressler and Fischer[14, 15] report a series of thirty-three cases; of the first nineteen the diagnosis was made in only three, and of the last fourteen it was missed in only three. Aside from their cases the diagnosis has been made in only seventeen out of 217 cases, including Levine's[18]; altogether the diagnosis has been made in thirty-one out of the 250 cases so far recorded.

CLINICAL ASPECTS

The clinical aspects of tricuspid stenosis are very well discussed by J. B. Herrick[7] and by Dressler and Fischer.[14] Only a few points in the symptomatology will be mentioned here. Dyspnea on exertion is practically always present if the lesion is advanced. Cyanosis is often, probably usually, present; while it may be very marked, it often is not.[23] There is always dilatation of the right auricle, with enlargement of the heart to the right. There is usually distention of the cervical veins, though this may not be great, and there is presystolic pulsation, of these veins with a large *a*-wave in the phlebogram. There is usually marked enlargement of the liver, with positive presystolic liver pulsation, detectable by palpation and by a liver pulse tracing. Auscultation of the heart must be very carefully performed, inasmuch as there is almost always a concomitant mitral stenosis, the signs of which often obscure those of the tricuspid stenosis. The mitral stenosis produces a presystolic or diastolic rough murmur at or near the apex, and the tricuspid stenosis a similar murmur at the xiphoid end of the sternum or just to the left or occasionally to the right of this point. The tricuspid murmur is often absent or indistinct,[21, 22] and even if present may be obscured by merging indistinguishably into the mitral murmur.[21, 22, 25] There may be two regions at which the murmur is at a maximum, one at the apical and one at the xiphoid region,[22, 25] with decreased intensity or even absence of the murmur between, or the two

murmurs may differ slightly in character, thus facilitating the diagnosis. The pulse is usually small. There may or may not be polycythemia.

If the right auricle fails completely or if there is auricular fibrillation, then the signs dependent upon auricular activity are absent, namely the presystolic (but not the diastolic) murmur, and the presystolic pulsations of the cervical veins[26] and the liver.

CASE REPORT

D. M., a white boy aged fifteen years, came to the cardiac department of the Mandel Clinic on September 14, 1932, complaining of dyspnea on walking a short distance and of moderate cough with bloody sputum. He had been reported in

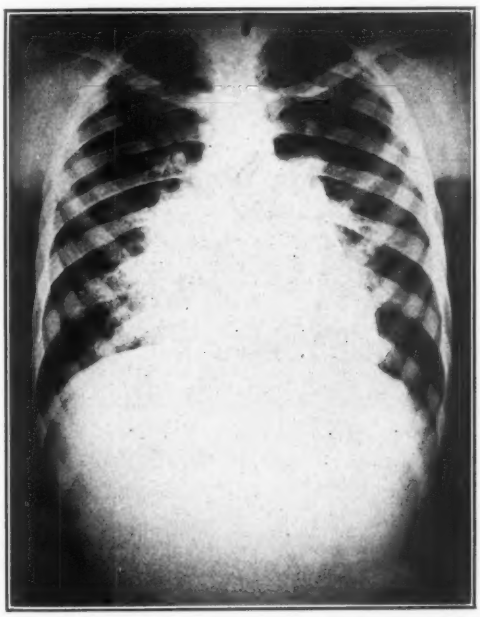

Fig. 1.—Distant heart plate, showing marked enlargement to the right and complete filling of the waist line.

good health by a camp physician in the summer of 1931 and had been apparently quite well until October, 1931, when he first noticed the above-mentioned symptoms. In December, 1931, he was told he had heart trouble. He was in bed from that time until July, 1932; during which interval he had been in two hospitals, had become weak, and had for some time had fever and marked edema of both legs. He left the hospital on July 22, 1932, with the diagnosis of rheumatic heart disease, mitral stenosis and insufficiency, enlarged heart. He had had scarlet fever and diphtheria in infancy, and measles and mumps later; the tonsils had been removed twice.

On September 14, 1932, the findings were as follows: The boy was thin, pale, and somewhat cyanotic. The cervical veins were somewhat full, and they pulsated visibly though only slightly. The lower right anterior chest and the right hypochondrium bulged somewhat, corresponding to the liver, which was felt 9 cm. below

the right costal border, down to the level of the umbilicus. There was slight but definite expansile pulsation of the liver, and pressure on the liver was accompanied by increased filling of the cervical veins. There was no pitting edema anywhere. The lungs seemed normal. Temperature was 98 degrees, pulse 104 and regular. Blood pressure was 136/74 mm. There was a presystolic thrill at the apex. The heart borders were 6 cm. to the right and 10.5 cm. to the left of the midsternal line, and the left border was straight. There was a rough presystolic murmur at the apex and also just to the left of the lower end of the sternum, while between these points the murmur was much less intense. There was a loud systolic murmur over the lower part of the heart. The second pulmonic sound was greatly accentuated. The boy was sent to Michael Reese Hospital with the diagnosis of chronic and subacute rheumatic myocarditis, mitral stenosis and leak, tricuspid stenosis and leak, hypertrophy and dilatation of the right ventricle and of both auricles, chronic passive hyperemia of the lungs and the liver.

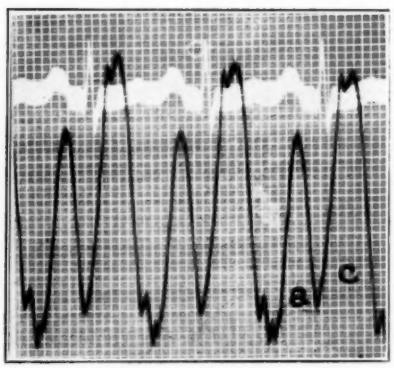

Fig. 2.

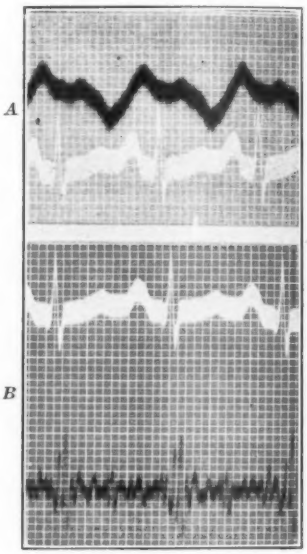

Fig. 3.

Fig. 2.—Simultaneous electrocardiogram and cervical phlebogram, showing very high *a*-wave.

Fig. 3.—Electrocardiograms with simultaneous liver puse tracing (*A*) and heart sounds (*B*).

During his stay in the hospital the boy developed edema of the lower extremities and the back, and ascites. At one time he had sharp pain, aggravated by respiration, in the left precordial region. The hemoptysis continued. Two days before death there were decreased resonance, suppressed breathing, and râles over most of the right and the lower half of the left lung fields. He died on November 16, 1932. During his last stay in the hospital there was occasional slight fever. The urine contained albumin but no erythrocytes. Two blood cultures showed nonhemolytic streptococcus, and a third was negative. A cervical phlebogram showed a high *a*-wave (Fig. 2), and a liver pulse tracing showed a presystolic wave* (Fig. 3). The final clinical diagnosis was as above with the addition of marked dila-

*These tracings were taken by Dr. Anne Bohning.

tation of the right auricle, intra-auricular thrombus, repeated pulmonary emboli with infarcts, marked heart muscle failure, anasarca, hydrothorax, ascites.

Autopsy was performed by Dr. Otto Saphir on the day of death. Both lower extremities were markedly edematous. The abdomen bulged. The skin and sclerae were slightly yellowish. Each pleural cavity contained about 700 c.c., the peritoneal cavity about 1500 c.c. of clear liquid. The heart was markedly enlarged and distended, weighing 625 grams. At the roots of the large vessels there were a few adhesions between the two layers of the pericardium. There were a few thrombi attached to the mural endocardium of both auricles. The endocardium in the region of the left ventricle corresponding to the interventricular septum was white and thickened. There was a small endocardial pocket, open toward the aortic valve, in about the midportion of the interventricular septum. The mitral valve leaflets were much thicker than normal, shrunken, and fused by confluence. The chordae

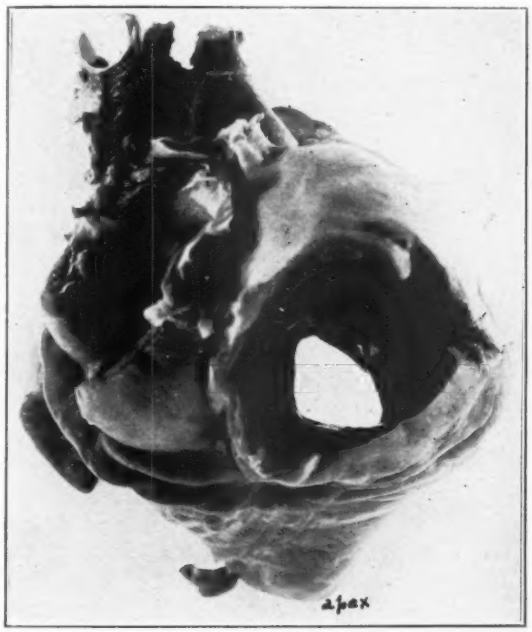

Fig. 4.—View of the narrowed tricuspid orifice from above.

tendineae were thickened, and many of them fused. The orifice of the mitral valve was only 4.2 cm. in circumference, much smaller than normal. The line of closure was studded with a row of beadlike vegetations. The aortic valve leaflets were somewhat thicker than normal; they were a little shrunken in the longitudinal diameter, but there were no adhesions betwen the cusps. The pulmonary valve was normal. The leaflets of the tricuspid valve were much thicker than normal, shrunken, and fused by confluence. Its orifice was only 7.1 cm. in circumference (Figs. 4 and 5). The coronary arteries were normal. The papillary muscles and the columnae carneae were thickened and flattened. The right ventricular wall was 4 mm. thick, the left 12 mm. The hypertrophy of the right ventricle was much more pronounced than that of the left. The right auricle was greatly dilated and its wall thickened up to 3 mm. Cut surfaces exposed by cutting the myocardium were gray, and showed several lighter gray and whitish spots and streaks. Histological examination of the myocardium revealed a marked increase in connective

tissue, in some places with hyalinization of the connective-tissue fibers. A very few sections revealed an infiltration of cellular elements (endothelial cells and occasional lymphocytes) in the perivascular spaces. In some fields these cells were in parallel rows suggesting Aschoff bodies.

The lower lobe of the right lung showed an organizing bronchopneumonia. In the left lower lobe there was a hemorrhagic infarct, and a branch of the pulmonary artery within this area was blocked by an embolus; there was a similar area in the right middle lobe. The liver was large and firm, weighing 1650 gm., and the seat of very marked passive hyperemia, with fatty changes. The spleen was enlarged, 600 gm., and firm. There were several yellow, wedge-shaped infarcts in the spleen. There was passive hyperemia, and there were several infarcts in the kidneys.

Fig. 5.—View of the narrowed tricuspid orifice from below.

DISCUSSION

Heart muscle failure with pronounced edema in this boy of fifteen years suggested strongly the presence of some abnormality besides mitral stenosis, inasmuch as cardiac edema in a child of this age is unusual. The most likely lesions were adhesive pericardiomediastinitis and a tricuspid lesion. There were no signs of the former, such as Broadbent's sign, inspiratory filling of the cervical veins, diastolic apical shock, fixation of the heart. Consequently we strongly suspected a tricuspid lesion. The enormous enlargement of the right auricle, and the pulsation of the cervical veins and the liver supported this opinion,

though without knowing the time of the pulse-waves the diagnosis of stenosis was not warranted.

The configuration of the heart and the murmurs confirmed the diagnosis of mitral stenosis. The presence of a presystolic rumble in the tricuspid area suggested tricuspid stenosis but did not prove it, inasmuch as the apical murmur in mitral stenosis may occasionally be transmitted to the sternum. But the almost complete absence of the murmur between the apex and the tricuspid area strongly indicated that the murmurs at those two areas were distinct and not due to one lesion.

SUMMARY

1. A review of the world literature to date reveals 250 cases of acquired chronic fibroplastic tricuspid stenosis, with correct ante mortem diagnosis in only 31.

2. The most important symptoms and signs of tricuspid stenosis are: Dyspnea on exertion, cyanosis, dilatation of the right auricle, distension of the cervical veins, presystolic pulsation of the cervical veins with a large *a*-wave in the phlebogram, marked enlargement of the liver with positive presystolic liver pulsation, a rough diastolic and presystolic murmur at the xiphoid end of the sternum. Those signs dependent on auricular activity disappear in auricular fibrillation or complete failure of the right auricle.

3. A case of tricuspid stenosis is reported, with correct ante mortem diagnosis, confirmed by autopsy.

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APPARATUS FOR THE DETERMINATION OF VENOUS PRESSURE IN MAN*

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VENOUS pressure is obtained in man by two methods, the direct and the indirect. The technic of the direct method requires the inserting of a large needle or trocar into a superficial vein of the forearm, and the connecting of the column of blood directly with a manometer upon which the pressure is read. The factors that make this procedure impracticable are the necessity of a sterile technic, possibility of the blood clotting, trauma to the vein, pain and other objections of the patient, and the inability to make repeated pressure determinations.

The indirect method depends upon the principle that the least pressure applied outside a vein required to actuate collapse will be practically equal to the pressure within the vein. Numerous instruments having either a water or a mercury manometer have been devised for this purpose, but they are expensive and repairs are difficult. The use of the water manometer is the most suitable, but the reading is hard to obtain because the column of water fluctuates to such a marked degree while pressure is being applied over the vein.

CONSTRUCTION

These objections have prompted the presentation of a modified apparatus for the determination of venous pressure in man by the indirect method. It consists of an ordinary thistle tube (1), over which has been tightly stretched a piece of a rubber glove (2), which has a small opening in its center (3), and is held taut and in place by a rubber band (4). The thistle tube is connected by rubber tubes and a T-tube (5) to a water manometer (6) and an ordinary rubber blood-pressure cuff (7). A pressure bulb(8) with an escape valve (9) is attached to the other opening of the rubber bag or cuff. The construction of the manometer is a glass tube bent in a manner (13) so as to have one end close to the bottom of a small glass reservoir (11). The manometer tube is connected to the reservoir through one of two openings in a rubber stopper (12), while an L-tube (10) through the other connects with the rest of the apparatus. The manometer tube and the reservoir are mounted upon a base board beside a meter stick (14). After the reservoir and the curved end of the manometer tube are partly filled with colored water, the meter stick is adjusted so that 0 is opposite the level of the water in the long arm of the tube. If the fluid level is a short distance above this point, the number of millimeters can be subtracted from the pressure reading.

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METHOD

The patient is placed in a semi-recumbent position with the right arm extended so that the hand is brought to a level with the right auricle of the heart. A large superficial vein of the hand is selected and surrounded by a ring of vaseline or water soluble jelly. The thistle tube is placed against the hand in such a manner that the opening in the rubber diaphragm is directly over the vein. In this position the vein can be watched through the glass thistle tube while air is pumped in by means of the pressure bulb. The reading is made in millimeters on the meter stick the instant the vein is collapsed.

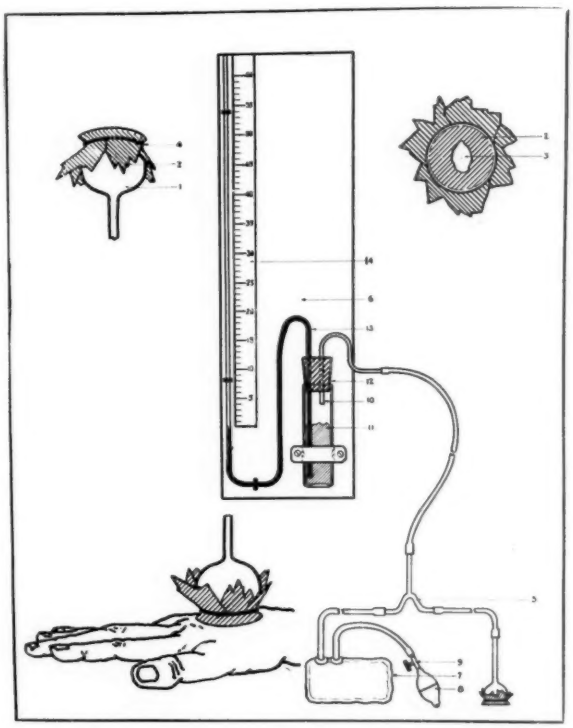

Fig. 1.—Diagram of venous pressure apparatus.

DISCUSSION

This instrument is inexpensive and can be made in any laboratory without requiring mechanical skill. The rubber bag or cuff acts as a buffer and allows the water to rise slowly and evenly in the manometer tube, thereby facilitating the ease and accuracy of the reading. The apparatus can be easily and rapidly repaired without requiring expensive parts. The apparatus is made portable by draining the water from the tube and the reservoir and refilling at the bedside.

DIGITALIS ASSAY WITH THE ISOLATED CAT HEART, COMPARED WITH OTHER METHODS*†

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WE HAVE used the simplified heart-lung preparation[1] of the cat for the bio-assay of 8 different preparations of digitalis bodies, and compared the potency, determined in this way, with the "pigeon-emetic" potency of the same preparations, the "pigeon-fatal" dose (6 preparations), as well as with the dose for the intact cat, and for the frog (5 preparations).

METHODS

Cat heart-lung preparations were made by ligating the azygos vein, the superior vena cava and the carotid and subclavian arteries of cats anesthetized with ether and given artificial respiration through a tracheal cannula. The inferior cava was occluded with a bull-dog clamp and the aorta by a hemostat at the level of the left subclavian artery. Blood was admitted into the heart from the inferior cava until the left auricle was full, but not distended, and the aorta pulsated strongly. Once the heart volume was satisfactory, the hemostat and the clamp on the inferior cava were not touched, and the volume of blood in the isolated circuit remained constant. Such preparations, kept at room temperature, lasted for two to five hours, and almost as long when kept at 37° C. The digitalis preparations, suitably diluted with 0.85 per cent NaCl solution, were injected with a tuberculin syringe and fine hypodermic needle into the left ventricle. Injections were made at five-minute intervals, beginning with 50 to 70 per cent of the estimated fatal dose and giving 10 per cent more at each injection. Ventricular fibrillation with persisting dilatation was taken as the end-point. It was noted that auricular stand-still, due to sino-auricular and nodal auricular block, occurred before ventricular fibrillation, usually after 70 to 90 per cent of the fatal dose. Ectopic ventricular beats occurred less often and were less striking.

"Pigeon-emetic" and "pigeon-fatal" doses (on intravenous injection) were determined in the usual way,[2] using groups of 7 pigeons for the final assay with doses 10 per cent ± the emetic dose, and 5 pigeons for the final assay of fatal doses. Thus, 20 to 25 pigeons were used for each emetic assay, and 12 to 15 for the fatal dose.

RESULTS

It was found that twice the fatal dose of strophanthin caused arrest of the isolated heart in forty to fifty seconds, while twice the fatal dose of digitoxin arrested the ventricles in one hundred and twenty to one hundred and fifty seconds. It was therefore considered proper to space injections at five-minute intervals. When assayed at 37° C. instead of

*Supported, in part, by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University.

†From the Departments of Medicine and of Pharmacology, Stanford University School of Medicine, San Francisco.

TABLE I

RESULTS OF BIO-ASSAY, USING VARIOUS METHODS

Maximum and minimum values for the 8 cats used in each assay are given in italics, average values in roman type. The ratios of emetic (E) to isolated heart (C) dosages, of pigeon-fatal (F) to isolated heart and to emetic doses are given.

PREPARATION	ISOLATED HEART DOSE PER KG. CAT MG. PER KG. C	ISOLATED HEART DOSE PER GM. HEART MG. PER KG.	PIGEON-EMETIC DOSE MG. PER KG. E	PIGEON-FATAL DOSE MG./KG. F	RATIO E/C	RATIO F/C	RATIO F/E
Digitalis purpurea tincture, Hatcher cat unit = 108 mg.	9.5 *7.2 to 12*	3.1 *2.1 to 4.3*	25.00	142.00	2.6	15.0	5.7
Digitalis lutea (an old tincture)	9.5 *7.4 to 11.7*	3.0 *2.4 to 3.9*	15.00	60.00	1.6	6.3	3.0
Digitalis purpurea (an old tincture)	16.0 *13.0 to 20.0*	5.0 *3.8 to 6.4*	40.00		2.5		
Digitoxin (Merck)	0.10 *0.071 to 0.15*	0.030 *0.022 to 0.044*	0.21	0.40	2.1	4.0	1.9
Strophanthin K	0.020 *0.017 to 0.024*	0.0065 *0.0053 to 0.0078*	0.04	0.20	2.0	10.0	5.0
Scillaren A	0.019 *0.0141 to 0.024*		0.03	0.43	1.6	23.0	14.0
Scillaren B	0.019 *0.013 to 0.022*		0.05	0.20	2.7	11.0	4.0
Scillaren, total glucoside	0.017		0.09	0.20	5.31	12.0	2.2
Digitoxin, 37° C.	0.055 *0.043 to 0.087*	0.018					
Strophanthin, 37° C.	0.016 *0.0151 to 0.0161*	0.005					

at room temperature, digitoxin was 82 per cent more active, strophanthin 25 per cent more active. The variation in dose per gram of heart was greater than that per kilogram of cat, due to the greater sensitivity of enlarged hearts to these drugs.[3] The variation between maximum and minimum dose per kilogram of 8 cats used for each preparation was 202 per cent in one group, but averaged only 68 per cent. This is distinctly less than the variation in groups of this size using the Hatcher

TABLE II

RELATIVE POTENCIES INDICATED BY DIFFERENT METHODS OF ASSAY. THE POTENCY OF DIGITOXIN FOR ANY ASSAY METHOD IS TAKEN AS 1

METHOD OF ASSAY	DIGITOXIN PER MG.	FOLIA DIGITALIS PER GM.	K-STROPHANTHIN PER MG.	SCILLAREN A PER MG.	SCILLAREN B PER MG.
Isolated cat heart at room temperature	1.0	10.5	5.00	5.3	5.3
Pigeon-emesis	1.0	8.4	5.25	7.0	4.2
Frog	1.0	7.1	4.00	4.0	6.7
Hatcher cat	1.0	3.6	2.00	1.35	2.0
Pigeon-fatal	1.0	2.8	2.00	0.90	2.0
Therapeutic for man	1.0	1.5			

method (whole cat). The results of all assays made by us are summarized in Table I; the relative potencies indicated by our assays and those of others in Table II.

COMPARISON OF VARIOUS METHODS OF ASSAY

The relative potency of digitalis bodies, assayed by various procedures, is given in Table II. The figures for frog and Hatcher cat doses were taken from Rothlin[4] and Fromherz;[5] those for the therapeutic dose for man from Eggleston.[6] It is obvious that two main groups of results are shown. One group (isolated cat heart at room temperature, "pigeon-emesis," frog) indicates that digitoxin is relatively weak in comparison with total digitalis glucoside and the glucosides from strophanthus and squills. The other group (intact cat, "pigeon-fatal") indicates that digitoxin much more closely approaches the other substances in potency. The therapeutic dose for man not only falls in the second group, but is most strikingly at variance with the results of assay by the first three methods.

A number of factors may account for the difference in potency of digitoxin and the other preparations when assayed by these methods. In the isolated heart, injected at five-minute intervals, the relative speed of fixation by the heart of digitoxin and of other glucosides is obviously important. The fixation of digitoxin is known to be accelerated as temperature rises. The differences between assay with cold preparations (isolated heart at room temperature, frog) or preparations in which the period of assay is short (isolated heart at 37° C.) and assay with slower or warmer preparations, might be due entirely to relative speed of fixa-

tion. At room temperature, strophanthin is fixed more than twice as rapidly as digitoxin, but even so, when the interval between injections is twice as long as needed for 50 per cent fixation and the initial dose is 50 to 70 per cent of the final dose, reached fifteen to thirty minutes later, it seems improbable that temperature and duration of the periods of assay can account for the differences in relative potency shown in Table II, although they undoubtedly play some part.

The difference in dosage for isolated hearts at 37° C. and intact cats points to differences in extracardiac fixation of the drug as one factor in causing differences in relative potency. The data in Table II suggest that digitoxin is fixed or destroyed by extracardiac tissues to a lesser degree than total digitalis glucoside, or the other glucosides tested, and further, that the fatal dose for the frog and emetic doses for pigeons are not affected by the extracardiac tissues. The intact frog, at room temperature, behaves much like the isolated cat heart as an indicator of digitalis potency.

The contrast between the "pigeon-emetic" assay and the "pigeon-fatal" dose assay is of great interest. In both tests digitalis bodies are injected into the vein of intact, warm birds, yet the fatal dose closely parallels the cat-fatal dose and the emetic dose parallels the dose for cold isolated cat heart, and diverges from the assay by killing pigeons or cats more even than does the frog assay. In these two pigeon methods, the rate of reaction of the various bodies with the tissues is of importance, for emesis occurs very promptly and, if it is to occur at all, does so within one to fifteen minutes. Death from average fatal doses occurs in five to sixty minutes after digitoxin, in five to ten minutes after strophanthin or scillaren. The average time is thirty-five minutes for digitoxin, seven minutes for the other glucosides. The period between injection and emesis, from average emetic doses, is eight and one half minutes for digitoxin; eight and three-tenths minutes for strophanthin, and the same or slightly longer for scillaren. Fromherz[5] has reported that the dose of digitoxin for cats is only one-half as great if no time limit is set, as when ninety minutes is taken for the period of assay. He found that the maximum effect was three to four hours after injection. Whether or not this is confirmed for cats, it does not hold true in pigeons, for practically all birds which survive average or less than average doses for one hour recover. Rarely death occurs seventy to one hundred and twenty minutes after injection, but the time allowed for assay (sixty minutes) will include almost all birds which will die, and, like the time (fifteen minutes) allowed for emesis, it equals nearly twice the average time for effect of average doses. In spite of the striking difference between duration for effect of emesis and for fatal action which distinguishes digitoxin from the other glucosides, it seems to us highly improbable that rate of fixation accounts

for the difference in relative potency indicated by the two pigeon methods of assay when the period of assay is long.

The difference between the results of assay by emetic and by fatal effect on pigeon, when ample time is allowed for the effect of the slowest preparation to be manifest, can be due only to a fundamental difference between the sites at which the two effects are produced. It seems highly probable that the fatal effect, produced entirely by action on the heart, varies with the amount of drug fixed or destroyed in the other tissues, while the emetic action is unaffected by the relative fixation of the drug in cardiac and extracardiac tissues. The difference in potency, indicated by emetic assay as compared with that indicated by fatal effect, as well as the fact that digitoxin which produces emesis as rapidly as other preparations, kills five times more slowly, indicates very clearly that emesis does not arise as a reflex from glucoside action on heart muscle. If it is of reflex origin, it probably arises from nerve endings wherever digitalis glucosides are taken up by the tissues and is unaffected by the speed or degree of cardiac absorption of the drug.

The fact that different methods of assay are not comparable was apparent in Eggleston's[6] early study of the relatively high potency of digitoxin given orally to patients as contrasted with the effects of digitalis and digitoxin on cats. His findings are included in Table II. The difference between methods of assay has often been emphasized. Extensive data have been reported by Knaffl-Lenz[7] and Fromherz[5] has recently added further data on the assay of digitoxin, digitalis glucosides and derivatives on frogs and cats. He found that total digitalis glucoside was much more toxic for frogs than for cats, as compared with digitoxin, and suggested that the total glucoside must contain a substance toxic for frogs but not for cats.

He found that a pure glucoside, digitoxin, was much more toxic for frogs than for cats, as compared with another pure substance, gitoxin. One cat unit of gitoxin equalled 50 frog doses, one cat unit of digitoxin equalled 100 frog units, and one cat unit of total glucoside equalled 150 frog units. Our assays with isolated cat hearts, and with pigeons, show that digitalis total glucoside, tested on one species, may be 2 or 3 times more potent in comparison with digitoxin by one method of assay than another. Such differences cannot be explained by species difference, and the facts brought out by this paper, as well as those by Fromherz, can only be explained by differences in site of action and fixation.

The differences in action of different bodies, such as scillaren, strophanthin, and digitoxin, have long been recognized; and it was clear that assay could be used only for controlling potency of products, not for predicting action in other assay methods or in clinical use. Even with preparations made by similar methods from a single species of plant, very different relative potencies may be indicated by different

methods of assay. Thus Hanzlik[2] had reported that the "pigeon-fatal" dose of one tincture was 2.6 emetic doses, that of another tincture 12 emetic doses. In Table I, one tincture of digitalis had identical effects, on isolated cat hearts, with another tincture, but the "pigeon-fatal" dose of one was 2.4 times that of the other. While some attempts to correlate assay by experimental methods with assay on man have been made, most of these are inadequate. Either too few patients were used, or the criteria of effect were not sharply drawn, or the different substances tested were too closely related in potency and had been assayed only by a single method. To be truly informative, clinical assay should be made with two substances, whose relative potency, measured by one method of bio-assay, differs from that given by another method. Eggleston's studies show that cat assay and therapeutic assay agree for infusions and tinctures of digitalis, but not for tinctures or infusions and digitoxin. In connection with the League of Nations Hygiene Organization, studies of the potency of three lots of folia digitalis were made in many laboratories and in two clinics.[7] In clinical assay by Gilchrist and Lyon[8] 99 trials were made on cases of auricular fibrillation, and 15 on one patient. The general results and those on one patient agreed in assigning relative potencies as follows—A:65; B:90; C:100. The assays on frog (Rana temporia) averaged as follows—A:50; B:94; C:100; those on other frogs, A:54; B:105; C:100. Infusions on cats gave—A:60; B:115; C:100; and tinctures tested on cats gave A:62; B:100; C:100. In other words, cat assay agreed with clinical assay about as closely as did frog assay. If, in Table II, the relative potency of digitoxin and that of digitalis leaf are compared, it is evident that the cat and "pigeon-fatal" doses parallel clinical effects, and the "pigeon-fatal" dose is more nearly parallel to clinical doses than any other.

The object of bio-assay is to permit the potency of drugs used in therapeutics to be maintained as nearly as possible at a constant level, and careful assay by any of the methods referred to in this paper, as well as several others, may be satisfactory for this purpose. The isolated cat heart, the "pigeon-emetic" method, and the frog method are more sensitive to differences in potency than are the fatal assays on pigeons or cats, or the therapeutic test on patients. Foxglove leaves of equal potency, assayed by any of these methods, will be closely related in their clinical potency. The choice of a method of assay would seem to rest largely on the ease and inexpensiveness with which many test animals can be used, for the accuracy of assay depends not merely upon carefulness but on the use of relatively large groups of animals.[9] The pigeon methods are relatively inexpensive and rapid, and although, with digitalis leaf, the emetic dose parallels effect on man,[10] it probably would be better to assay preparations for both emetic and fatal effects,

and to reject, for therapeutic use, preparations varying by more than 25 per cent from the standard in either type of assay.[11]

SUMMARY

1. A method of assay using a simple heart-lung preparation of the cat for determining cardiac activity of digitalis bodies is described and compared with other methods of assay, particularly the emetic and fatal dose for pigeons.

2. There is strong evidence that, in pigeons, the emetic phenomenon is in no way related to the cardiac action of digitalis substances.

3. There is a close parallel between results of assay by isolated cat heart, frog, and pigeon emesis, and between assay by fatal effect on whole cats, or pigeons, and therapeutic effects on man.

4. Frog assay or pigeon emetic assay is more sensitive to differences in potency than is cat or pigeon fatal effect assay.

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Department of Clinical Reports

VENTRICULAR TACHYCARDIA, RATE OF 300, FOLLOWING THYROIDECTOMY

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THERE continues to be a difference of opinion concerning the origin of the cardiac impulse in cases with very rapid ventricular rates. Although the criteria for differential diagnosis are rather confusing in this case, we believe it to be one of ventricular tachycardia, with a rate faster than any heretofore published.

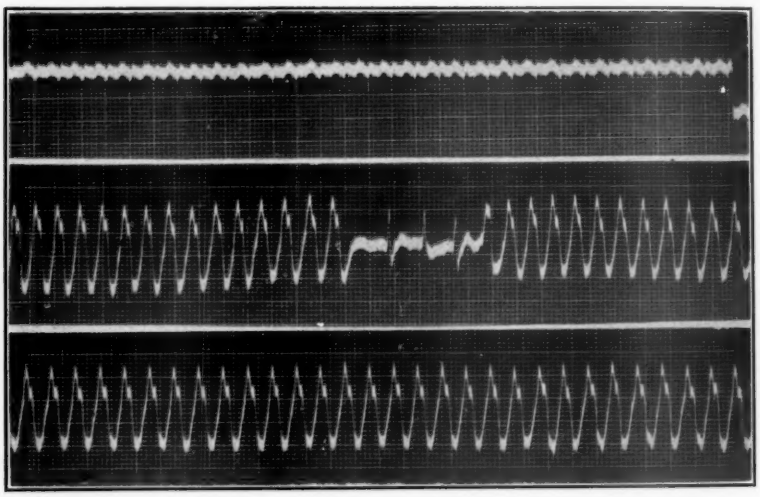

Fig. 1.—September 15, 1932. During paroxysm of ventricular tachycardia.

A white American male, aged fifty years, in 1930 complained of "nervous indigestion" and palpitation of the heart on exertion. He was advised at a clinic that his trouble was due to the mental strain connected with his occupation, and that he should have more relaxation in the open air to correct a spastic colon.

He first came under observation in June, 1931, complaining of troublesome gastrointestinal symptoms and of heart consciousness and palpitation, but no dyspnea, edema or cough. Emotional disturbances and exertion were about equal in producing his symptoms. He was accustomed to taking his own pulse and said that he had found it as high as 120. He had not lost weight. He had a tendency to watery stools and continued to have indigestion, whether he ate sparingly or forced himself to eat a rational diet.

The man was pale and extremely apprehensive. He had cold bluish hands and was perspiring profusely in the arm pits. His reflexes were all hyperactive. The heart was found to be normal, except for the rate, which was 92 per minute. The blood pressure was 170 mm. Hg systolic, 70 mm. Hg diastolic. This systolic hypertension, as well as the elevated pulse rate, was attributed to excitement and apprehension. There was practically no thyroid tissue palpable. The urine was normal. Blood examination

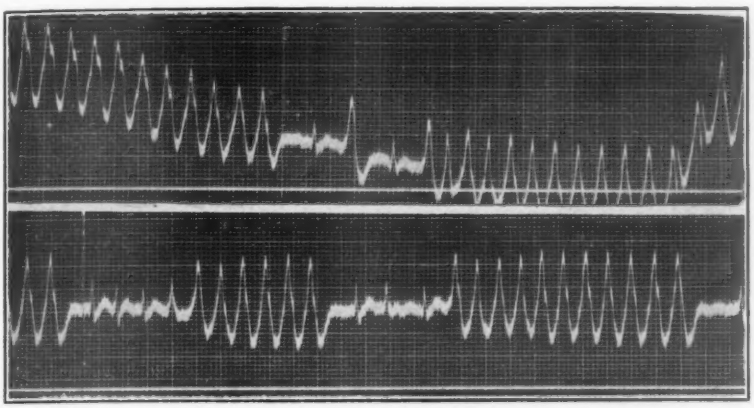

Fig. 2.—Lead II. Deep breath holding during paroxysm.

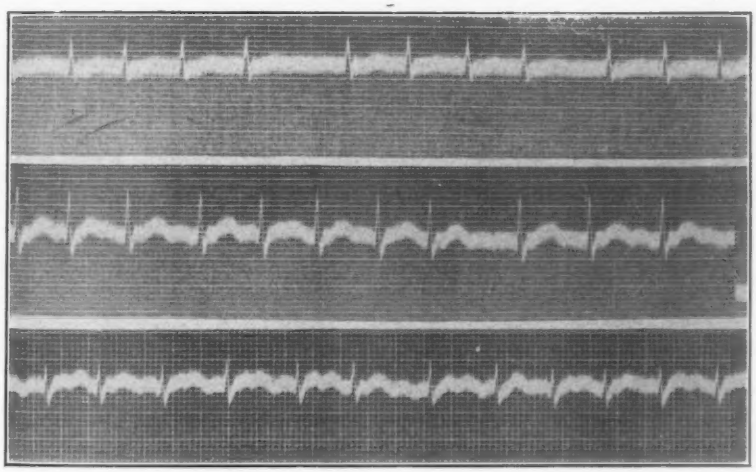

Fig. 3.—Auricular fibrillation twenty-four hours after paroxysm.

showed a hemoglobin of 70 per cent; R.B.C. 3,660,000; W.B.C. 6,550, with a normal differential count. The Wassermann test was negative.

On the second examination ten days later, the pulse rate was 76 and the blood pressure was 138-70. One month later the patient was greatly encouraged and regarded himself as well.

Four months later, October 21, 1931, at the insistence of an insurance company, an electrocardiogram was made which showed a rate of 70 and was essentially normal (Fig. 4).

On November 30, 1931, he came for reexamination complaining of a return of his former symptoms which he dated definitely to the day he received a letter from the insurance company saying that he had been refused insurance. His anorexia had returned. The gastrointestinal discomfort had reappeared, and he was unable to eat without being distressed.

In February, 1932, the patient was seen by a colleague. His complaints were all related to his gastrointestinal tract. After careful examination and repeated study this physician was of the opinion that the patient's cardiovascular system was not abnormal. Following this there was a remission of symptoms, the patient voluntarily stated that he felt better than he had for two years.

About six months later, September 1, 1932, the patient showed a marked and abrupt change in his condition without any known exciting factor. He became more nervous and apprehensive than he had ever been before and for the first time was tremulous.

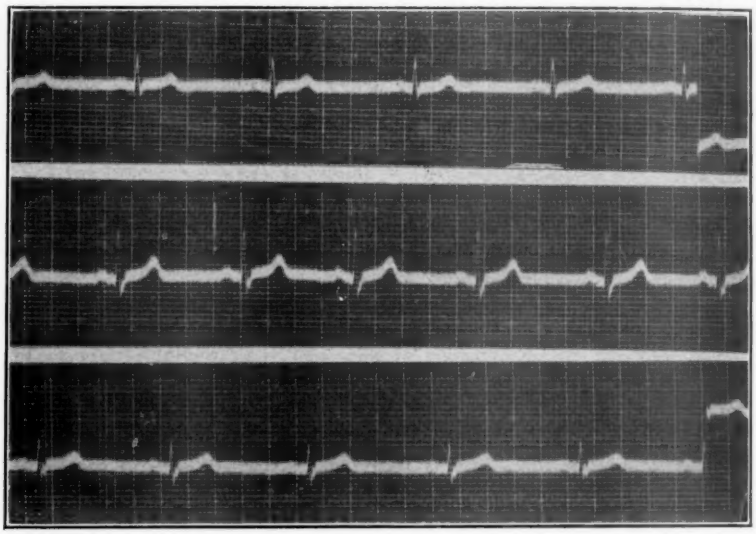

Fig. 4.—October 26, 1931. One year before thyroidectomy.

There was a continuously rapid pulse rate, a sharp weight loss, and a marked increase in basal metabolic rate (plus 43 per cent). The diagnosis of Graves' disease was then made.

A bilateral thyroidectomy was performed September 14, 1932, at 8 A.M. The pulse rate at operation varied between 110 and 120. Until thirty-six hours after operation his postoperative course was uneventful, except for the extreme apprehension, which seemed to be part of the personality make-up of this individual. The nurse recorded the pulse at 7:35 P.M. the day following the operation as 120. Ten minutes later the patient collapsed, and his pulse rate could not be counted. The skin was cold and clammy, and the blood pressure was unobtainable. Electrocardiograms were taken two hours after the onset of the attack. The patient at this time looked extremely ill. The pulse was almost imperceptible. The blood pressure was 60 mm. Hg systolic, 40 mm. Hg diastolic. The rate was so rapid as to be uncountable. The heart was pounding vigorously at a regular rhythm, interrupted at varying intervals from five minutes to less than a minute by short periods of a different rhythm. The pulse at the wrist during the short interruptions was more perceptible than during the prevailing

rhythm. The patient complained of discomfort in the chest and profound weakness. He was given morphine sulphate, gr. ¼ at 8:30 P.M. Pressure on the eyeballs and on the carotid sheath produced no change in rate or rhythm. Deep breath holding, which feat the patient was unable to perform very satisfactorily, produced more frequent interruptions in the prevailing rhythm and an increased rate. Six grains of quinidine sulphate were given at 10:15 P.M. At 1:00 A.M., about five hours after the onset of the tachycardia, the patient's condition seemed critical. There were signs of pulmonary edema. Quinine hydrochloride, 7½ grains, was given intravenously. Immediately after the administration of this drug the rhythm changed to auricular fibrillation with a ventricular rate of about 150. He became very much better clinically and from then on improved rapidly. Within forty-eight hours the rhythm was normal. Quinidine sulphate, grains 4 twice a day, was continued for several days, as well as digitalis. The patient left the hospital in a wheel chair on October 3, 1932.

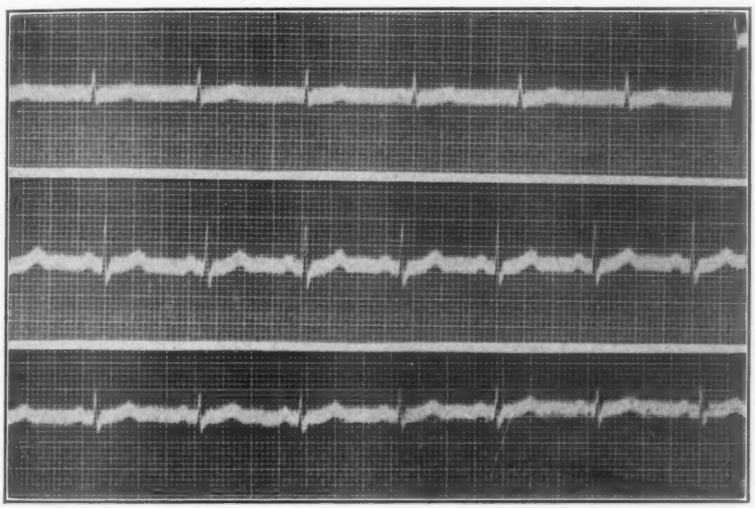

Fig. 5.—September 21, 1932. Normal rhythm one week after thyroidectomy.

DISCUSSION

The interruptions of the extremely rapid rhythm are supraventricular in origin and probably represent auricular fibrillation. During these periods of irregularity it will be noted that the ventricular rate continues to be about 250, beyond which rate, according to previously reported cases, the auricles and ventricles usually become dissociated. It is possible that the notching on the descending limb of the R-waves may represent auricular impulses to which the ventricle was able to respond up to the rate of 300, which if true would establish this as a case of auricular flutter with one-to-one conduction.

In favor of the ventricular origin of the tachycardia, however, is the undoubted ventricular characteristic of the complexes which dominate the picture and the prompt response to quinine therapy. In addition to this, the clinical observation that the pulse volume was much stronger

during the short periods of interrupted rhythm merits consideration, since premature ventricular contractions often fail to be palpable at the wrist. Furthermore, the frequent interruption of a prevailing rhythm is more characteristic of ventricular than auricular tachycardia. It is probable that the notching on the descending limb of the R-waves represents auricular beats produced by retrograde conduction of impulses from the ventricle to the auricle.

Scott's criteria[1] on ventricular tachycardia are difficult to apply in this case. He believes with Lewis[2] that the paroxysm starts abruptly and ends abruptly, and that to be of ventricular origin it must begin with a premature systole of ventricular origin and end with a diastolic pause comparable to that encountered after a premature systole. In our records the interruption of the prevailing rhythm did not occur in the same manner each time, nor did it recur following any constantly typical complex.

Wiggers[3] states that "the only other way in which a ventricular tachycardia can be diagnosed with certainty is to establish that undoubted P-waves occur at a rhythm which is slower and unrelated to the ventricular beats." This does not seem to be true in this case.

The effect of deep breath holding during the paroxysm is interesting. The rate increased from 300 to 325. The type of QRS complex was definitely changed, and the periods of interruption were more frequent.

Mention should be made of the possibility that the palpitation from which this patient suffered in 1930 might have been due to hyperthyroidism. Certainly evidence sufficient to warrant operative interference was lacking until a few weeks before an unusual and almost fatal disturbance in the heart's mechanism occurred. It is interesting to note from serial electrocardiograms how completely the myocardium has recovered. Clinical data confirm this fact.

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COMPLETE HEART-BLOCK OF THIRTY YEARS' DURATION*

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THE diagnosis of complete heart-block usually conveys the idea of rather severe, diffuse myocardial injury, and in the majority of instances this impression is correct, especially if the complete auriculoventricular dissociation is the result of arteriosclerosis. Several cases of complete heart-block of rather long duration have been reported, and in several instances the heart-block has in no way interfered with the activities of the patients. In Ellis' series,[1] he reported one case of twenty-four years' duration, two of nine years' duration, and one of seven years' duration. None of these four patients had symptoms or any other evidence of any cardiac insufficiency. White[4] reported two cases in which the patients had persistent, complete heart-block for fourteen and fifteen years respectively, and their heart-block had in no way interfered with their activities. In a series of thirty-seven cases of complete heart-block reported by Willius,[5] the average duration of the history indicating auriculoventricular dissociation was two and nine-tenths years, and the longest duration was fifteen years. Willius[6] also has reported a case, however, of twenty-two years' duration. Russell-Wells and Wiltshire[3] followed a case of intermittent heart-block for twelve years, and the patient died of carcinoma of the cecum. Harris[2] reported a case in which complete heart-block had been present for twenty-eight years, and the patient had enjoyed good health during this whole period. Keith described a case in which there was a history of complete heart-block for eighteen years.

REPORT OF CASE

A white janitor, forty-three years of age, came to The Mayo Clinic complaining of rectal fistula and some shortness of breath on severe exertion.

At the age of thirteen years he had had an acute illness accompanied by extremely sore throat, and what apparently were bilateral retropharyngeal abscesses had been lanced. His temperature at that time had been as high as 103° F. He had been given diphtheria antitoxin; there were cases of diphtheria and scarlet fever in the neighborhood where he lived. His two sisters had been given prophylactic doses of diphtheria antitoxin at the same time. His physician had not been sure whether the patient had diphtheria or not. About one week after his acute illness had subsided his cardiac rate became very slow, and he again was confined to bed for several weeks. His pulse rate had been below 40 each minute at the time referred to, and had remained between 30 and 40 most of the time through all the subsequent years. Tonsillectomy had been performed about ten years before he came

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to the clinic, and his pulse rate had been slightly faster for a short time following the operation. He stated that after his spell of acute illness he would become short of breath on severe exertion. Because of this he could not run and play as well as other children could. While he was a child he had learned just how much he could do without getting short of breath. With severe exertion he would become light-headed and dizzy, although with moderate exercise he encountered little difficulty. As far as he was able to tell when he was examined at the clinic, his condition was no worse than it ever had been since his illness. He had never fallen nor lost consciousness.

The man was well developed and well nourished; he weighed 195 pounds stripped. His blood pressure was 124 mm. of mercury systolic and 76 mm. diastolic. His temperature was normal, and his pulse rate was 44 each minute. His voice sounded as though he had an acute cold. Heart tones were somewhat distant, but of good quality. The cardiac rhythm was regular and there were no murmurs. There was a draining sinus in the median line, 1.5 cm. posterior to the anus. The remaining portion of the physical examination gave essentially negative results. His blood count was well within normal limits, and urinalysis and flocculation tests for syphilis

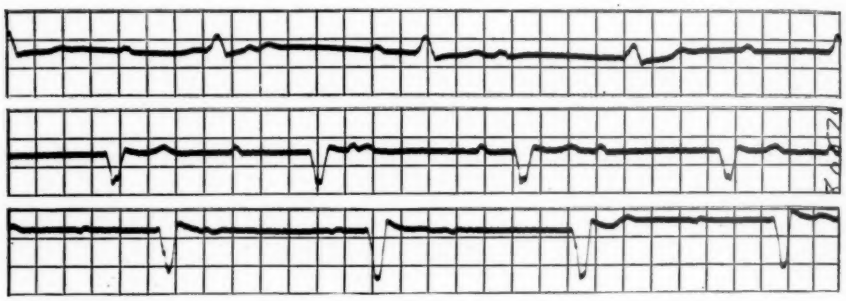

Fig. 1.—Complete A-V dissociation: auricular rate 69 each minute; ventricular rate 41.

gave negative results. Roentgenological studies of his heart did not reveal enlargement. The electrocardiogram revealed a ventricular rate of 41 each minute and an auricular rate of 69, with complete auriculoventricular dissociation. Aberrant QRS complexes and marked left ventricular preponderance were evident.

COMMENT

The long duration of the history of complete heart-block in this case is extraordinary. From the history it is impossible to be certain what acute infection the patient had when he was thirteen years of age. It may have been diphtheria or septic sore throat; either or both could have produced heart-block. I believe there is very little doubt that heart-block had been present constantly since the onset, even through the short period following tonsillectomy when he noticed that his cardiac rate was slightly faster than it usually was; he was not sure what the rate was during this short period.

His cardiac efficiency was about as good when I examined him as it had been since his illness thirty years before. If he restricted his activities somewhat, he had practically no difficulty.

It is to be presumed that the lesion responsible for the block was some acute inflammatory process which by cicatrization brought about the permanent interruption of the functions of the auriculoventricular bundle.

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Department of Reviews and Abstracts

Selected Abstracts

Paul, John R., and Leddy, P. A.: The Social Incidence of Rheumatic Heart Disease. A Statistical Study in Yale University Students. Am. J. M. Sc. 184: 597, 1932.

The incidence of rheumatic heart disease in a group of 7914 undergraduate students of Yale University has been found to be 8.2 per thousand as compared with 15 per thousand which is an average figure obtained from statistics of comparable age groups of individuals in other walks of life. Among the men in this group who had attended expensive boarding schools, the incidence was 5.8 per thousand as compared with 12.5 per thousand among those in high schools.

The contention that rheumatic fever is a disease which finds a lower incidence among people of ample means finds support in these observations. According to the methods employed, the factor of poverty does not, however, seem to be as important a predisposing rôle in determining the incidence of rheumatic heart disease as it does in clinical tuberculosis.

Wetherby, Macnider: Chronic Arthritis. A Clinical Analysis of Three Hundred and Fifty Cases. Arch. Int. Med. 50: 926, 1932.

Three hundred and fifty consecutive cases of chronic arthritis have been subjected to a clinical analysis. In this series, 68.57 per cent of the patients were women and 31.43 per cent were men. The peak of onset occurred in the fifth decade for both sexes. The duration of symptoms in this series was over one year in 88 per cent and over five years in 55 per cent of the cases.

Monarticular involvement, in a strict sense, was present in only 5 of the 350 cases. A study of the joints involved showed the knees to be affected most frequently in 82.8 per cent of all cases. Other joints commonly involved were the following: fingers, 61.1 per cent; ankles, 58.3 per cent; spine, 57.1 per cent; shoulders, 57.1 per cent; wrists, 50 per cent; hips, 44.6 per cent; and elbows, 42.6 per cent.

There are certain definite sex differences in the distribution of the joints affected, there being a significantly more frequent involvement of the fingers, hands and toes in women and of the spine, hips and feet in men. There is also a marked difference between the sexes in the joints most severely involved, the fingers being the most seriously affected in 16.6 per cent of the women and in only 0.9 per cent of the men, while, on the other hand, the spine was most severely affected in 20 per cent of the men and in only 5.8 per cent of the women.

A study made of the percentage distribution of involvement of the joints by decades showed no striking differences in the distribution in arthritis coming on at different decades of life.

In 32 patients with chronic arthritis there was an acute febrile onset which was similar to the clinical description of rheumatic fever. Such an acute onset was much more frequent in the younger age group. Of this number, 6 (18.7 per cent) had definite rheumatic involvement of the heart. The incidence of rheumatic disease of the heart in the total group of 350 patients was 7 (2 per cent).

Probable sources of streptococcic infection were known to precede the arthritis in 102 cases (29.1 per cent). The more common inciting sources were dental infection, sinusitis, acute respiratory infection, tonsilitis, puerperal sepsis and the puerperium without known infection. Polyarthritis immediately followed definite trauma in 12 cases.

Subcutaneous nodules were sought in 300 consecutive arthritic patients and were found to be present in 94 cases (31.3 per cent). The incidence of subcutaneous nodules was determined for the various age groups; they were found to be present in over 40 per cent of the patients over fifty years of age. Such nodules were found in patients with various clinical and roentgen-ray findings.

Roentgen-ray examinations of all painful joints in 60 consecutive cases have shown a pure type of involvement in only 33.3 per cent, a mixed type in 58.3 per cent and no positive findings in 8.3 per cent of the cases.

Schwartz, Sidney P., and Jezer, Abraham: Transient Ventricular Fibrillation. The Clinical and Electrocardiographic Manifestations of the Syncopal Seizures in a Patient With Auriculoventricular Dissociation. Arch. Int. Med. 50: 450, 1932.

A clinical and electrocardiographic study was made of the syncopal seizures in a patient with auriculoventricular dissociation. More than a hundred electrocardiograms obtained during such seizures revealed the cardiac mechanism to be due to transient ventricular fibrillation.

The natural periods of transient ventricular fibrillation in the patient have varied in duration from only a few seconds to six minutes each, and as many as two hundred and seven attacks of unconsciousness have been observed during a period of twenty-four hours with spontaneous revival. During a period of four months' observation, not a single day passed without the patient experiencing at least one attack.

The premonitory periods preceding a transient seizure of ventricular fibrillation of the ventricles have been variable. They consisted at first of alternate premature beats of the ventricles, which increased the basic ventricular rate. These were followed shortly by irregular periods of recurring groups of aberrant ventricular oscillations, only the first few of which could be heard at the apical region of the heart or felt at the radial pulse.

Pallor of the face and momentary loss of consciousness followed the appearance of these recurrent groups of ventricular oscillations when, during their presence, the pulse disappeared for more than eight seconds but for not more than twelve.

A major attack of unconsciousness with cyanosis, stertorous breathing and convulsions took place when the heart sounds and pulse disappeared for at least twenty but not less than forty seconds. The electrocardiograms made during these periods invariably revealed ventricular fibrillation.

The frequency of the ventricular oscillations during the periods of transient ventricular fibrillation varied from 250 to 500 per minute.

Spontaneous revival from a seizure of ventricular fibrillation was usually ushered in by the appearance in the electrocardiograms of a postundulatory pause, which was followed by an intermediary idioventricular rhythm, as a rule, with an increasingly irregular rate before the restoration of the basic ventricular rhythm.

It is important to appreciate that syncopal seizures in patients with auriculoventricular dissociation are much more commonly associated with transient periods of ventricular fibrillation that has been suspected hitherto.

Rational therapy for the prevention of syncopal seizures in patients with auriculoventricular dissociation depends upon an intimate knowledge of the cardiac mechanism underlying these seizures.

Bedell, Caroline C.: Auricular Flutter With 1:1 Response. Bull. Johns Hopkins Hosp. **52:** 225, 1933.

Paroxysmal attacks of 1:1 response occurring during the course of auricular flutter are described in 24 cases. Three of these cases are reported for the first time with electrocardiograms and tabulated analysis of the records obtained. An autopsy report on one of the cases is included. The remaining 21 cases have been gathered from the literature.

One-to-one flutter occurs most frequently in the fifth decade of life. It has not been observed above the age of fifty-seven years, in contrast to other forms of auricular flutter which may occur after the age of seventy years. In other respects the etiology is similar. One-to-one paroxysms occurred during the course of established auricular flutter in which a high grade of block is not established, often with increasing ease and frequency. The attack begins abruptly following exertion. Extreme weakness, shortness of breath and palpitation are the usual manifestations. Syncope, precordial pain and congestive failure may occur. After minutes or hours, the attack subsides gradually. Attacks have followed the administration of quinidine, as well as the combination of atropine and avertin.

The attacks of syncope and possibility of congestive failure during frequent paroxysms somewhat modify the general prognosis in flutter. Digitalis effectively prevents 1:1 paroxysms by increasing the A-V block. During quinidine administration, the patient should be in bed on account of the possibility of paroxysms.

Sigler, Louis H.: Functional Bundle-Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation. Am. J. M. Sc. **185:** 211, 1933.

Bundle-branch block complete and partial may be functional in origin caused predominantly by vagal inhibition and fatigue. Restoration of normal QRS complexes in such cases may be accomplished by removal of vagus inhibition where vagal effect is the underlying cause and by local rest where fatigue is the cause.

A parodoxical case is reported where left vagal stimulation apparently removed rather than caused such block. The underlying functional disturbance in this case was apparently fatigue of one of the bundle branches which was sufficiently relieved by increased vagal slowing to permit normal bundle-branch conduction. Abnormal QRS complexes occurred after as long a rest as 0.56 of a second, and normal complexes were restored by additional rest of 0.08 second.

Graybiel, Ashton, and Sprague, Howard B.: Bundle-Branch Block; An Analysis of 395 Cases. Am. J. M. Sc. **185:** 395, 1933.

An analysis of 395 cases of bundle-branch block is presented. It is felt that diagnosis of bundle-branch block can only be made with certainty by the use of the electrocardiogram. From the standpoint of diagnosis and prognosis, it is important to determine its presence in cardiac patients.

Bundle-branch block almost invariably indicates serious organic disease of the heart, usually coronary disease; the average duration of life of the 223 fatal cases in this series after the discovery of the conduction fault was one year and two months, but 85 other patients are still alive after an average of two years and eleven months following the discovery of the bundle-branch block. Partial bundle-branch block must be regarded clinically as equally significant with complete bundle branch block, the prognosis in both being essentially the same.

Conner, Lewis A.: A Discussion of the Rôle of Arterial Thrombosis in the Visceral Diseases of Middle Life, Based Upon Analogies Drawn From Coronary Thrombosis. Am. J. M. Sc. **185**: 13, 1933.

Attention is called to the fact that whereas thrombosis in the arteries of the heart and of the brain is known to be common and is easy of clinical recognition, almost nothing is known concerning the symptoms of arterial thrombosis in the abdominal viscera. Nevertheless, the frequent occurrence of degenerative changes in the arteries of the pancreas, kidneys, spleen and mesentery indicates that thrombosis in these vessels cannot be rare.

The failure to recognize attacks of arterial thrombosis in the abdominal organs must be due in part to the inherent difficulties of diagnosis, but is almost certainly also due partly to our failure to have the possibility of such attacks in mind and to have accumulated pertinent evidence.

An attempt is made to construct a framework of diagnosis for arterial thrombosis in the kidney, pancreas, spleen and mesentery by utilizing certain symptoms associated with thrombotic infarction in the heart (fever, leucocytosis) and those which result from infarction due to embolism in the kidney, spleen and mesentery.

It seems probable that when both internists and pathologists begin seriously to seek for evidences of such thromboses and to correlate their findings, the difficulties of diagnosis will be found to be not insurmountable and the lineaments of the respective clinical pictures will gradually emerge from the present obscurity, much as have those of the diagnosis of coronary thrombosis.

Coombs, Carey F.: Prognosis in Coronary Thrombosis. Bristol Med. Chir. J. **49**: 277, 1932.

A sad interest attaches to this paper, the proofs of which were returned by Dr. Coombs on the day before his death from coronary thrombosis. In the same journal are printed a photograph and obituary of Dr. Coombs.

The remarks contained in the paper are based on notes from 144 patients seen by the author. Of the 144 patients, one out of three died in, or shortly after, the attack. He states that the prognosis depends more upon the severity of the attack than upon the background of the patient. He believes that data derived from the state of the peripheral circulation on examination give important information. The immediate danger in cardiac infarction is that the heart will not be able to fill the peripheral circulation. It is this that makes extreme pallor so ominous a symptom. Measurement of the blood pressure also nearly always gives reliable evidence of the extent to which the efficiency of the peripheral circulation is impaired. The most significant feature is the fall in the systolic tension. Also a most direct measure of the efficiency with which the damaged heart is filling the vessels is the pulse pressure. While a low pulse pressure, especially below 25 per cent, is a bad sign, it is not possible to claim that patients with a wide pulse pressure are sure to recover. The author states that if he were compelled to rely for prognosis on one sign alone, it would be the pulse pressure that he would choose.

He points out that with increasing experience it is possible to make a diagnosis of coronary thrombosis in relatively mild cases, and when these are included in a study, the number of patients who recover can be expected to increase.

Symposium on Chronic Myocarditis. New England Heart Association. I. Warren, Shields: The Pathology of Chronic Myocarditis. New England J. Med. **208**: 573, 1933.

The author discusses only those changes that can be recognized by the pathologist and which are found in certain of the cases of chronic myocarditis. These changes are due principally to impairment of the coronary circulation associated with arterioscle-

rosis or atherosclerosis. He points out, too, the great frequency with which fibrous myocarditis occurs in diabetic autopsies. He believes this is due to the marked degree of arteriosclerosis shown by these cases.

II. Christian, Henry A.: Diagnosis of Chronic Nonvalvular Cardiac Disease (Chronic Myocarditis). New England J. Med. **208:** 574, 1933.

Terminology is unsatisfactory. Chronic nonvalvular cardiac disease, if one understands that the pericardium is not concerned, is satisfactorily descriptive. Chronic myocarditis carries the idea of inflammation with connective tissue proliferation and this usually is lacking. However, in classical Greek the termination "itis" did not mean inflammation of but merely "concerning, of or about," and in this classical sense chronic myocarditis is a justified title.

Chronic myocarditis constitutes half of cardiac patients in an adult clinic: incidence increased with advancing years; rare before 45 except after hypertension; may occur at any age from the cradle to the grave.

Symptoms are those of cardiac insufficiency of any cause.

Physical examination shows cardiac enlargement; in obese or emphysematous patients x-ray pictures may be needed to determine the size of the heart. Very rarely the heart is not enlarged.

A murmur, systolic in time, often is present, but there may be no murmur; if present, may be of any intensity or distribution; basal diastolic murmur sometimes is heard, due to dilatation of aortic or pulmonic orifice.

Rhythm is regular or irregular; extrasystoles are most frequent; auricular fibrillation is next in frequency; bundle-branch block or intraventricular block is quite often shown in electrocardiogram; bundle-branch block is often detectable by inspection and palpation as pointed out by John T. King, Jr.

Hypertension is often present and is an important etiological factor, but in some patients is never present. Arteriosclerosis, especially of coronary arteries, has the same relation; syphilis is not an etiological factor except exceedingly rarely.

In a high percentage of cases, clinical diagnosis is confirmed at autopsy.

III. Jackson, Henry: Treatment of Nonvalvular Heart Disease of Middle and Old Age. New England J. Med. **208:** 574, 1933.

The author discusses the various measures which are recognized to be of value in preserving such patients from further strain on their heart. He also discusses briefly the use of digitalis, nitroglycerine and similar drugs.

Brown, Madelaine R.: A Study of the Pathogenesis of Myocardial Fibrosis ("Chronic Fibrous Myocarditis"). Am. J. M. Sc. **184:** 707, 1932.

The material for this study consists of 1000 consecutive autopsies of which 110 described areas of scar tissue in the myocardium. It was not evident from a study of these cases that infectious diseases or toxines gave rise directly to fibrosis of the myocardium, although they may be concerned in producing arteriosclerosis of the coronary arteries. Direct invasion of the heart muscle in syphilis and rheumatism plays a minor rôle in the pathogenesis of myocardial scarring.

Disease of the coronary arteries which was present in 70 of the 110 cases causing either infarction or more slowly produced ischemic necrosis of the muscle fibers, is advanced as the important etiological agent of myocardial scarring ("chronic fibrous myocarditis").

Lisa, James R., and Ring, Alfred: Myocardial Infarction or Gross Fibrosis. Analysis of One Hundred Necropsies. Arch. Int. Med. **50:** 131, 1932.

A series of 100 autopsies showing myocardial infarction or gross myocardial fibrosis, consisting of 10.6 per cent of 942 autopsies performed is analyzed. Thirty-two of these cases showed definite recent cardiac infarction, while 68 showed fibrotic patches interpreted as probable old infarction. Eighty-three were in males, 17 in females. The average age of all patients was 60.8 years. The youngest was twenty-eight years old, the oldest eighty-three years. The average weight of the heart was 519 gm. Most of the lesions were located in the left ventricular wall or involved the left ventricle and interventricular septum, but in 14 cases the lesions were confined to the septum alone. Approximately 83 per cent showed moderate to marked coronary sclerosis. Coronary thrombosis was noted in 24 cases; in 3 there was thrombosis of both the left and the right coronary artery. Mural thrombosis occurred in 34 cases, in 16 of which there had been recent infarction. Aneurysm of the left ventricle was noted in 5 cases; chronic adhesive pericarditis occurred in 10. Ten patients had positive Wassermann reactions, while 9 others showed evidence of vascular syphilis at autopsy. Hypertension occurred in approximately 60 per cent of the cases. In 24 cases in which electrocardiograms were taken, the most frequent change was abnormality of the T-wave, which occurred in 23. Seventeen cases showed abnormalities of the QRS complex, 5 auricular fibrillation and 1 complete heart block. Fifty-six cases presented cardiac symptomatology, while in the remaining 44 the symptoms were referred to some other organ. Eight of the 12 sudden deaths in the series were due to recent cardiac infarction.

Bach, Francis, and Bourne, Geoffrey: Permanent Organic Cardiovascular Disease After Thyrotoxemia. Quarterly J. Med. **1:** 579, 1932.

The authors have studied 36 patients who had previously suffered from active thyrotoxicosis in whom no signs of present thyroidal activity were discoverable when reexamined for cardiovascular abnormality.

It is concluded from this study that thyrotoxicosis does not produce permanent changes in the normal heart. It may produce an additional myocardial change in hearts affected by some other cause of myocarditis, or predisposed to arteriosclerosis. The disease may initiate hypertension presumably in individuals predisposed to that condition.

Book Reviews

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM, INCLUDING THE CARDIAC ARRHYTHMIAS. By Harold E. B. Pardee, M.D. Pp. 295, with 74 illustrations. New York, Paul B. Hoeber, Inc., 1933, third edition.

The fact that this excellent manual has now required a third edition is eloquent testimony both to the merit of the book as a clinical guide and to the rapid growth of the science of clinical electrocardiography. The latter has made necessary extensive rewriting of many of the chapters and the addition of much new material. It is interesting to note that in the discussion of the localization of ventricular premature beats and of the myocardial lesions giving rise to bundle-branch block, the more recent views as to localization are accepted by the author.

This new edition fully merits a continuance of the popularity earned by the earlier ones.

INFARTO CARDIACO. By Pedro A. Castillo, M.D., Profesor de Clinica Medica, Havana. Pp. 351, with 99 figures, 2 colored plates. Havana, Talleres Tipograficos "La Propagandista," 1931.

Professor Castillo's book on cardiac infarction should be of interest and value to Spanish-speaking physicians. No new facts or startling theories are expressed, but the different aspects of coronary thrombosis are discussed from the author's experience and from his wide knowledge of the literature, and reports of 29 cases —some with post-mortem observations—are included. The material is arranged in orderly sequence; the volume is generously illustrated; and there is a long bibliography. Evidences of hasty proof reading mar an otherwise excellent book.

E. H.

NOUVEAU TRAITE DE MEDICINE. FASCICULE X. PATHOLOGIE DE L'APPAREIL CIRCULATOIRE (COEUR ET VAISSEAUX). Vol. III, pp. 720. Masson & Cie. Paris, 1933.

This volume—the work of Drs. Bickel, Courcoux, Dumas, Durand, Gaugier, Goyet, Gravier, Legry and Lelong—deals with diseases of the blood vessels and completes the series of three volumes on the pathology of the circulatory system. More than half the pages are devoted to aortitis, aneurysm, arteritis and arterial tension, with shorter sections on thrombo-angiitis obliterans, periarteritis nodosa, arterial embolism and diseases of the veins. The work is carefully prepared and well illustrated and in general plan is similar to the earlier volumes.

E. H.